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*"The moment one gives close attention to any thing,
even a blade of grass it becomes a mysterious, awesome,
indescribably magnificent world in itself."*

Henry Miller (1891 – 1980)
American author

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Prenatal Diagnosis of Chromosomal Abnormalities—Shifting Paradigm

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It is very likely that in 10 years time, invasive prenatal diagnostic tests like amniocentesis and chorionic villus sampling (CVS) will join the club of forgotten obstetric procedures like vaginal breech delivery and rotational forceps delivery. In 1968, Henry Nadler¹ and his team were the first to report prenatal diagnosis of trisomy 21 from full karyotyping of cultured amniocytes obtained by amniocentesis. Over the next 40 years, both amniocentesis and CVS became commonplace diagnostic tools to obtain fetal cells for antenatal diagnosis of chromosomal abnormalities in high-risk pregnant mothers. The methods of screening and identifying the high-risk mother have changed over time. Initially, invasive testing methods like amniocentesis and CVS were offered to women of advanced maternal age (typically women above 35 years). It was soon realised that age was a poor screening method for fetal chromosomal abnormalities, especially Down syndrome, that most deliveries occurred in mothers aged less than 35, and while their individual risk is lower, this group makes a significant contribution to missed diagnoses. Various screening tests were therefore introduced. The most sensitive and most recommended is the first trimester combined screen (FTS), which includes ultrasound-measured fetal nuchal translucency and serum biochemistry at 11 to 14 weeks gestation. The FTS detects 85% to 90% of all fetuses with Down syndrome but has a significant false positive rate (3% to 5%). These 3% to 5% of pregnant mothers require invasive diagnostic tests to confirm the diagnosis, which will be truly positive in only 3% to 4% of these screen-positive women.

Fetal Genetic Material in Mother's Blood

However, the whole paradigm of prenatal screening and diagnosis of chromosomal abnormalities started to shift with the identification of cell-free fetal DNA (cffDNA) in maternal circulation.² The discovery of this promising source of fetal genetic material propelled forward commercial

exploration of non-invasive prenatal testing (NIPT) at a tremendous pace. The origin of these cffDNA is believed to be from trophoblastic fragments entering maternal circulation. The dissolved DNA in maternal plasma is a mixture of fragmented maternal and fetal genomic DNA (10% to 20%) and becomes detectable 5 weeks after conception. The concentration of the fetal fraction (cffDNA) increases with gestational age and falls with increasing maternal weight. The sea of background maternal DNA, however, poses a great challenge for assessing fetal chromosomal status from the small amount of cffDNA. The total absolute amount of fetal DNA is typically less than 1 µg in 20 ml of maternal blood and unfortunately, there is no reliable way to separate the ostensibly similar fetal cell-free DNA (cfDNA) from the maternal cfDNA at the present time. However, many different technical approaches have been used to circumvent this and a number of non-invasive prenatal tests have become commercially available since 2011. The rapid availability of the tests have been made possible by the development of very rapid DNA sequencing and computing capability of matching hundreds of millions of DNA fragments and sequences in hours.

Looking for the Needle in the Haystack

The most commonly used aneuploidy testing technique randomly amplifies all available cfDNA in the maternal plasma sample with polymerase chain reaction (PCR) and then uses a DNA sequencing method called massive parallel sequencing (MPS) or next-generation sequencing (NGS). The chromosomal origin of each DNA fragment or “read” is then determined by comparing its sequence with known chromosome-specific human genome sequences. The relative amount of each chromosome's DNA is then compared in this MPS approach. Trisomies are detected based on excess DNA from a specific chromosome, relative to all other chromosome pairs. Mathematical modelling methods are used to determine thresholds (deviations from

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the expected mean amount of particular chromosomes DNA), which is strongly associated with the diagnosis of aneuploidy. The absolute increase in the trisomic chromosomal DNA is, however, dependent on 2 important facts—firstly, the proportion of fetal fraction in the maternal plasma cfDNA. Hence, these tests may not yield results before 9 weeks gestation and may be insufficient for prenatal diagnosis in obese women. Secondly, the differential amplification efficiency of DNA fragments of different chromosomes. The variability of amplification is dependent on the guanine-cytosine (GC) content, and GC content is lower in chromosomes 13 and X than in chromosomes 21 and 18. Hence, the detection of trisomy 13 and monosomy X is less efficient. However, this problem of amplification has been answered by mathematical methods correcting for each chromosome's GC content. Majority of commercial tests available (MaterniT21 test from Sequenom, veriFi from Verinata/Illumina, iGeneScreen from Inex and the NIFTY test from BGI) are using the MPS method.

A second cfDNA testing strategy uses a more targeted approach rather than the “shot-gun” approach of the MPS method. In this technique, selectively amplified genomic regions of target chromosomes are sequenced, rather than all available cfDNA. These specific sequences from target chromosomes are then quantified to determine if there is trisomy-related overexpression. This approach reduces the number of sequences to read, which accelerates reporting time and allows use of benchtop sequencers, thereby reducing cost. The Harmony test from Ariosa utilises this approach. This test has a high sensitivity for trisomy 21 and 18, but considerably less sensitivity for trisomy 13.

A third approach uses targeted amplification of chromosome-specific polymorphic loci (SNPs). It then integrates maternal and paternal (if available) allelic data to model a set of hypotheses based on monosomy, disomy or trisomy for each chromosome and incorporates all possible inheritance patterns and crossover locations. Bayesian statistical analysis is then used to assign a probability to each hypothesis, and select the most likely hypothesis. This approach claims to have a low false positive result. Since this technique does not require a reference chromosome, it is equally sensitive for all autosomal trisomies, sex chromosomal aneuploidy and triploidy detection. The Panorama test from Natera utilises this approach.

Many other approaches are being developed and many more companies are developing newer tests and waiting in the wings. A number of cell-free fetal nucleic acids (cffNA) tests are already reporting on common deletions and will soon be detecting common insertions and single-gene mutations.

Application in Clinical Practice

While the technology used by different tests vary, they all have very high sensitivity (approximately 99%) for the detection of trisomy 21. These tests also have a very high specificity for detection of trisomy 21 (above 99%). This was initially tested in a number of studies with high-risk samples. These were mostly validation studies by the testing companies and utilised case-control formats with known abnormal samples or prospective cohort studies in high-risk populations. A meta-analysis of these studies confirmed the efficacy of these cffDNA tests in high-risk singleton pregnancies.³ Pooled detection rates and false-positive rates for trisomy 21 were 99.0% (95% CI, 98.2 to 99.6) and 0.08% (95% CI, 0.03 to 0.14), respectively. Detection rates for trisomy 18 and 13 were also well above 90% with very low false positive rates (below 0.2%). However, detection rates for sex chromosome aneuploidies, like Turner syndrome, were slightly lower than 90%.

Given the performance of NIPT in high-risk pregnancies, many professional societies such as the International Society for Prenatal Diagnosis (ISPD), the National Society of Genetic Counselors (NSGC), and the American College of Obstetrics and Gynecology (ACOG) approve, though do not proactively recommend cffDNA testing only for high-risk women. These professional bodies advise the deployment of NIPT as a “secondary” screening tool for women who are deemed to be at increased risk due to age, history or positive primary screening tests. NIPT using cffDNA is still a screening test and an abnormal result must always be confirmed with invasive prenatal diagnosis.

While the results from the studies in high-risk cohorts were very encouraging, until recently, it was quite unclear about the performance of NIPT in a general average-risk population. Recently, Bianchi et al⁴ published the results of a multicentric cohort comparison of standard aneuploidy screening and cffDNA test in a low-risk population with a mean maternal age of 29.6 years. The authors found that both the tests achieved 100% detection rate for trisomy 21 and 18, but the cffDNA test was 10 times better in predicting cases of Down syndrome compared to the standard blood test and ultrasound screening, and 5 times better in predicting trisomy 18. The number of false-positive results was also greatly reduced, thereby reducing the number of unnecessary invasive tests. Dr Bianchi commented that “9 out of 10 women who are currently being referred for further testing would not need invasive tests”. Given the result of this study and another large study from China,⁵ it is likely that cffDNA testing will increasingly be offered to all pregnant women within the next few years as a primary screening tool. Already, the most recent guidelines from the American College of Medical Genetics (ACMG) do not distinguish between ‘high-risk’ and ‘low-risk’ populations, although

they continue to recommend confirmatory invasive testing for definitive diagnosis. Indeed, the appeal of these non-invasive tests to the consumer are such that the industry has managed to popularise these tests even before large prospective trials, and before regulatory and academic bodies are able to issue any guidelines regarding the use of these tests. Test companies have pursued various strategies to build consumer demand including reaching out to expectant mothers through the effective use of social media like Facebook and YouTube.

However, patients need to be informed that tests using cffDNA do not provide information about some disorders that are identified through standard combined ultrasound and serum biochemistry screening. False positives of cffDNA tests do occur. Possible underlying causes for such discordance could be confined placental mosaicism, maternal chromosomal abnormalities and very rarely, an occult maternal malignancy.

Pandora's Box?

A concern is the push from industry to introduce less validated tests in the screening package, in order to surge ahead in the race. Companies are hurrying to add various chromosomal abnormalities, such as microdeletions associated with DiGeorge syndrome, to the list of disorders for which they can test. On one hand, routine screening for microdeletions could enable more families to prepare for children with special needs. However, the physical and mental effects of such microdeletion syndromes are not always entirely predictable. A positive test result might lead to unnecessary invasive tests and, in some instances, prompt difficult decisions for families that receive such diagnoses. There are more difficult ethical issues on the horizon. In 2010, Lo et al⁶ reported that the entire fetal genome was represented in short cffDNA fragments in the maternal plasma and suggested that the reconstruction of substantially complete inherited complement was technically attainable. Genome-wide inherited and de novo variations can be determined prenatally without risk to the mother or fetus.⁷ The problem no longer lies with the technique, but with the meaningful translation of the findings and ethics. A serendipitous finding and discovery of genetic variants of uncertain significance will certainly lead to challenging clinical situations.

Conclusion

Without doubt, introduction of NIPT based on cffDNA testing is the big-bang development that has taken place in obstetrics in the 21st century. It is rapidly moving from a secondary screening tool for high-risk pregnant patients to a primary screen for all pregnant women. Unfortunately,

cffDNA testing is still expensive and cost remains prohibitive for many women, although the cost is heading downwards. The outcome of several ongoing patent lawsuits in the United States between all the major test companies may alleviate or exacerbate this cost issue. In Singapore, these tests have been available since 2013, but at a cost almost similar to an invasive diagnostic test. However, there are no local laboratories performing the test here and hence, the maternal plasma samples need to be sent to laboratories overseas. Establishment of a local laboratory would certainly help to reduce cost and minimise turnaround time. Unlike invasive diagnostic tests such as amniocentesis and CVS, there are no government subsidies or Medisave cover for NIPT at present. As a direct consequence, NIPT is becoming a popular screening test for the privately cared, while low-income families infrequently take up the test. This raises concerns that unless subsidies are made quickly available, it may lead to significant disparity in access to optimum prenatal care.

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Are Pregnant Women Adequately Equipped for Autonomy in Pregnancy Screening?

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Abstract

Introduction: Aneuploidy screening is widely practised in the field of obstetrics in current times. This study thus aims to gain an insight on pregnant women's knowledge and risk perception of Down syndrome and first trimester screening (FTS), as well as their views on various potential pregnancy outcomes and how these may affect their decision-making processes. **Materials and Methods:** A cross-sectional questionnaire-based qualitative study of consecutive 50 women choosing to undergo FTS at KK Women's and Children's Hospital (KKH), Singapore was conducted. The women completed a questionnaire after their FTS pretest counselling session. Basic knowledge of Down syndrome and FTS as well as participants' risk perception with regards to various cut-off values used in FTS were examined. Patients' views of various potential pregnancy outcomes were also studied. **Results:** Most patients had good retention and comprehension of what FTS entailed after a FTS counselling session at the KKH Antenatal Monitoring Clinic. However, knowledge of the risks of invasive diagnostic testing was poor. Patients also did not possess an adequate understanding of FTS risk values. With regards to risk perception, patients had very different views on acceptable pregnancy outcomes and what constituted a high-risk FTS value to them personally. A significant number of women were concerned even at medically low-risk values of 1:500 and 1:1000 in FTS. The majority of patients viewed highest detection rate followed by a lowest false positive rate as the more important factors impacting their choice of a Down syndrome screening test. **Conclusion:** This study demonstrates the diversity of pregnant women's risk perception, risk aversion and participation in decision processes when there are 2 different values in competition. The study also highlights our patients' gaps in knowledge and lack of understanding of risk values used in FTS.

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Key words: Choice, Decision-making, Pregnancy, Prenatal test, Risk assessment

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Introduction

The concept of first trimester screening (FTS) to evaluate the risk of fetal aneuploidies was first introduced in 1997 by Orlandi et al.¹ The Fetal Medicine Foundation, London, has refined and popularised this screening test that uses a combination of maternal age, nuchal translucency (NT) thickness and biochemical markers, namely beta-human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein A (PAPP-A), at 11 to 13⁺⁶ weeks gestation to determine one's risk of having a pregnancy with aneuploidies and a broader range of pregnancy disorders.² Since its introduction, many developed nations around the world have been offering this screening test to pregnant

women as part of routine antenatal care, with many patients choosing to undergo it. However, there is relatively little published knowledge on whether these patients understand their own motivations for choosing to undergo the test, and the potential impact of the results of the screening test on their pregnancy, be it emotionally in terms of anxiety regarding the results, or physically if invasive diagnostic testing is done following a high-risk FTS. In addition, we also recognise that as individuals, one's perception of risk may differ from another, and as such, their decision-making processes and preferences may differ accordingly as well.

This study aims to assess our patients' knowledge on Down syndrome screening and examine their individual risk

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perception, risk aversion, preferences with regards to what they view as important in a Down syndrome screening test, as well as their views on selected pregnancy outcomes to see if these factors in combination affect their decision processes. This information may then allow us to better counsel patients before their decision to undertake aneuploidy screening, as well as to tailor post-screening recommendations based on patients' personal risk perception and preferences.

Materials and Methods

This study was a qualitative cross-sectional study conducted between March 2012 to July 2012. All women presenting for antenatal care in KK Women's and Children's Hospital (KKH) were offered assessment of risk for trisomy 21, 18 and 13 by a combination of maternal age, fetal NT thickness, and maternal serum free beta-hCG and PAPP-A at 11 to 13⁺6 weeks gestation as per local guidelines' recommendations. Patients who had chosen to undergo FTS for aneuploidies were invited to participate in the study. Patients were reassured that their participation or non-participation would not affect their antenatal care in any way. In addition, none of the researchers were involved in the direct care of the patients. Approval of the study was attained from Singhealth's Centralised Institutional Review Board (CIRB), and waiver of consent was obtained.

All eligible women were given a detailed information sheet explaining the background and aims of the study immediately after they had undergone their FTS pretest counselling session. During this pretest counselling session, patients were counselled by trained nurse counsellors with regards to the risk factors for Down syndrome, implications of a child with Down syndrome, high risk cut-off values for aneuploidy screening, as well as the available options for subsequent management of a pregnancy with a high-risk screening test result, including chorionic villus sampling (CVS) or amniocentesis. This being a qualitative study, it was decided that an arbitrary number of 50 patients would be enrolled into the study over the 2-week period.

A questionnaire was designed to assess the knowledge of patients with regards to aneuploidy screening and Down syndrome, and explore their preferences of what factors they regarded as important in a Down syndrome screening test. Risk perception of patients was also examined by presenting to them various FTS reported risks of Down syndrome in the form of numerical values and pictorial representations on a diagram depicting 1000 women with the affected women (pregnancies with Down syndrome) highlighted in red, with subsequent questions on whether they would be concerned and if they would do invasive testing at these reported Down syndrome screening risks. A question which aimed to examine patients' personal views regarding possible pregnancy outcomes was also included in the questionnaire,

with patients being asked to rank in order of preference which pregnancy outcomes were most or least acceptable to them. The questionnaire was given out to participants of the study immediately after FTS pretest counselling was completed. Multilingual purpose-trained staff were on standby to answer any queries or clarifications patients may have regarding the questionnaire to allow for a more complete collation of responses. Data of the survey was collated and analysed using Microsoft Excel statistical analysis package.

Results

Study Population

Fifty patients were interviewed over a period of 2 weeks at the Antenatal Monitoring Centre at KKH. The characteristics of the study population are summarised in Table 1.

Table 1. Characteristics of Study Population and Singapore's Population

	Study Population n = 50 (%)	Singapore's Population* (%)
Race		
Chinese	35 (70)	74.1
Malay	5 (10)	13.4
Indian	8 (16)	9.2
Others	2 (4)	3.3
Age		
<35 years	42 (82)	-
>35 years	9 (18)	-
Type of housing		
HDB 1/2 room flat	4 (8)	4.6
HDB 3/4/5 room/ executive flat	43 (86)	77.5
Condominium	2 (4)	11.2
Terrace house/bungalow	0 (0)	5.7
Missing	1 (2)	-
Educational attainment		
High school graduate or less	23 (46)	77.2
Attained a college degree	27 (54)	22.8
Religion		
Christianity	8 (16)	18.3
Islam	7 (14)	14.7
Hinduism	6 (12)	5.1
Buddhism	16 (32)	33.3
Taoism	2 (4)	10.9
Free-thinker	11 (22)	17
Parity		
Primiparous	32 (64)	-
Multiparous	16 (32)	-

*Census of Population 2010 Statistical Release 1. Demographic Characteristics, Education, Language and Religion. Department of Statistics, Ministry of Trade and Industry, Singapore. Available at: http://www.singstat.gov.sg/publications/publications_and_papers/cop2010/census_2010_release1/cop2010sr1.pdf. Accessed 23 December 2013.

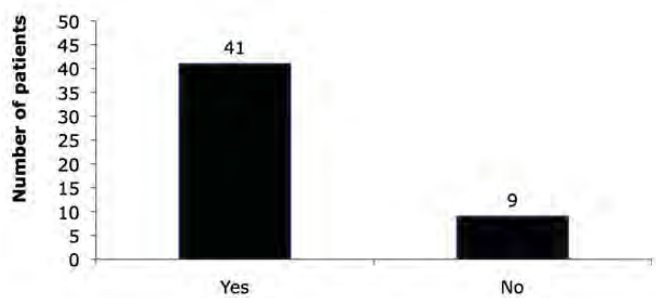


Fig. 1. Number of patients who responded to the question, “Is maternal age related to an increased risk of Down syndrome?”.

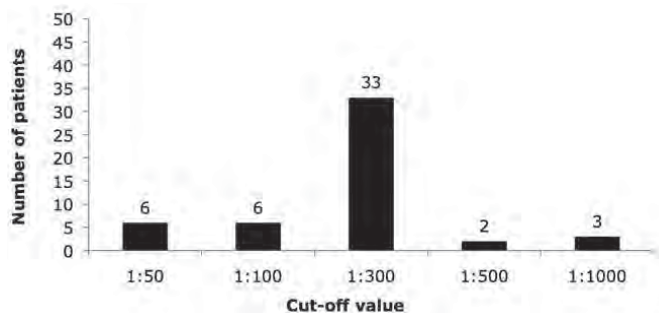


Fig. 2. Number of patients who responded to the question, “What current value is considered “high-risk” for Down syndrome in the FTS test in KKH?”.

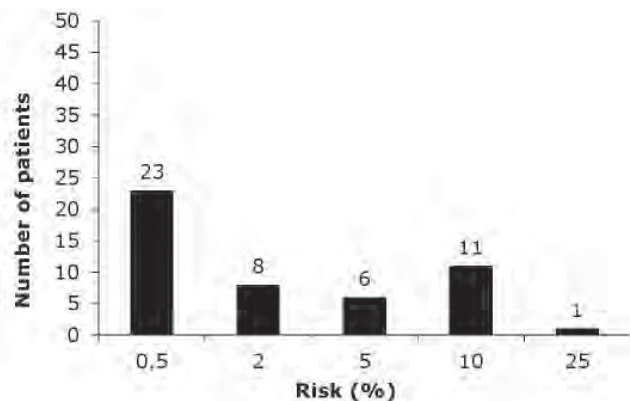


Fig. 3. Number of patients who responded to the question, “What is the risk of miscarriage associated with CVS/amniocentesis?”.

Knowledge

In general, most patients had good retention and comprehension of what FTS entailed after a FTS counselling session at the Antenatal Monitoring Clinic. A total of 41 patients correctly identified that increased maternal age was a contributing factor in the risk for Down syndrome in pregnancy (Fig. 1). Also, 33 patients (66%) could recall KKH’s cut-off value for high-risk as 1:300 (Fig. 2).

However, patients’ knowledge of the risks of invasive diagnostic testing was poor. Eleven (22%) patients thought the risk of miscarriage was as high as 10% (Fig. 3). Patients also did not possess an adequate understanding of FTS risk values. When asked what a high-risk value of 1:50 in FTS meant to them, 34 patients had the incorrect impression that a high-risk value equated to the fetus either having Down syndrome most or all of the time (Fig. 4).

Preferences

Patients were asked to rank in order of preference which factors were important to them in a Down syndrome screening test (Fig. 5). The 4 options given were “lowest false positive rate”, “highest accuracy”, “fastest results” and “lowest cost”. A total of 32 patients chose “highest accuracy” as the most important factor in a Down syndrome screening test. This was followed by 7 patients who ranked “lowest false positive rate” as the most important factor. Only 1 patient regarded cost of the screening test as the most important determining factor for a Down syndrome screening test.

Risk Perception

Patients were shown various FTS risks of Down syndrome in the form of numerical values and pictorial representations on a diagram depicting 1000 women with the affected women (pregnancies with Down syndrome) highlighted in red. They were asked if they would be concerned and if they would do invasive testing at these risks.

In our study, it was observed that the higher the reported risk of Down syndrome based on the FTS test, the larger would be the number of patients who would choose to do invasive testing for Down syndrome. However, 17 and 12 women expressed that they would still be concerned at a risk of 1:500 and 1:1000 respectively. Also, some patients opted for invasive testing even at low-risk values of 1:500 and 1:1000. It was also noted that the number of women who would undergo invasive diagnostic testing for each FTS risk quoted was smaller than the number of women who were concerned for each corresponding FTS risks (Fig. 6).

In a subgroup analysis of the 14 patients who had a correct understanding of FTS risk values as shown in Figure 4, 8 out of 14 were still concerned at risk of 1:500 and 5 out of 14 were still concerned at risk of 1:1000.

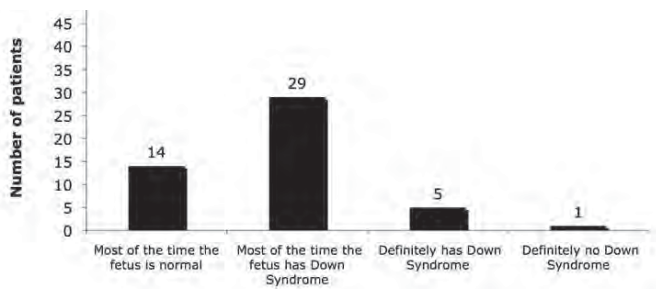


Fig. 4. Number of patients who responded to the question, “If FTS result is high risk e.g. 1:50, what does it mean for the pregnancy?”.

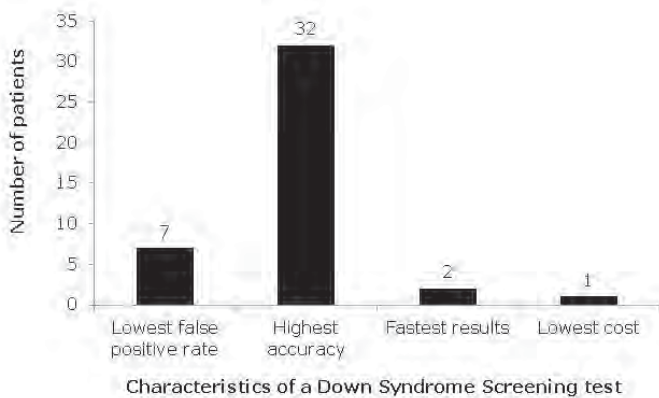


Fig. 5. Number of patients who responded to the question, “Which of the following is most important to you in a Down syndrome screening test?”.

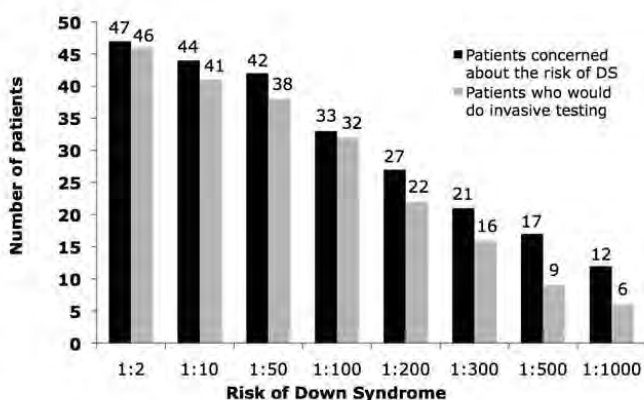


Fig. 6. Number of patients who responded to the question on the “Relationship between Down syndrome risk and threshold for concern and invasive testing”.

Desired Pregnancy Outcomes

The question in Figure 7 aimed to assess patients' personal views of various possible pregnancy outcomes. Of the 50 patients involved in the survey, 39 patients ranked the outcomes in entirety, with 11 patients leaving blanks for certain options and were thereafter excluded from this aspect of the analysis. The most desired pregnancy outcome chosen by all patients was predictably “having a healthy child”. Interestingly, the choice of least desired pregnancy outcomes varied greatly among the patients, as represented in the graph in Figure 8. The majority (26 out of 39 patients) felt that having a child with Down syndrome was their least desired pregnancy outcome of all the given options. However, 8 patients ranked “losing a fetus with Down syndrome through a chosen abortion” as their least desired pregnancy outcome. In addition, in a subanalysis of results with specific reference to the second and fourth options, 12 patients ranked having a child with Down syndrome as more acceptable than losing a healthy fetus through a miscarriage as a complication of chorionic villus sampling (CVS) or amniocentesis.

Discussion

This study on FTS is focused on patient autonomy, and analyses Down syndrome screening in particular. The College of Obstetricians and Gynaecologists, Singapore (COGS) recommends that all women, regardless of age, should be considered to be at risk for fetal aneuploidy and should be offered screening for Down syndrome, and they should be made aware of the availability of screening tests for Down syndrome and other chromosomal abnormalities.³ This recommendation is similarly reflected in many other countries' guidelines, such as that of the National Institute for Health and Care Excellence (NICE),⁴ American Congress of Obstetricians and Gynecologists (ACOG),⁵ and joint Human Genetic Society of Australasia (HGSA) and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)⁶ guidelines. However, adequacy on the exercise of patient autonomy has not been examined widely. As advocates for our patients, we need to understand our patients' motivations for undergoing complex screening, and assess whether they understand the potential psychological, physical and emotional impact of doing so. It is also important for us to make sure that our patients' knowledge of Down syndrome and other aneuploidies are accurate and up-to-date such that they may be able to make informed decisions regarding screening so as to achieve true patient autonomy, which is one of the 4 important principles in the field of biomedical ethics.⁷

Currently, patients in KKH undergo counselling prior to deciding whether or not to undergo the FTS test. They are presented with information regarding the various risk factors

Rank in order the below possible pregnancy outcomes from 1 to 7, 1 being the pregnancy outcome you wish **most** to happen, 7 being the pregnancy outcome you wish **least** to happen.

_____ Having a healthy child

_____ Having a child with Down syndrome

_____ Losing a healthy fetus through a spontaneous miscarriage

_____ Losing a healthy fetus through a miscarriage as a complication of chorionic villus sampling or amniocentesis

_____ Losing a fetus with Down syndrome through a spontaneous miscarriage

_____ Losing a fetus with Down syndrome as a complication of an amniocentesis or chorionic villus sampling

_____ Losing a fetus with Down syndrome through a chosen abortion

Fig. 7. Ranking question on pregnancy outcomes.

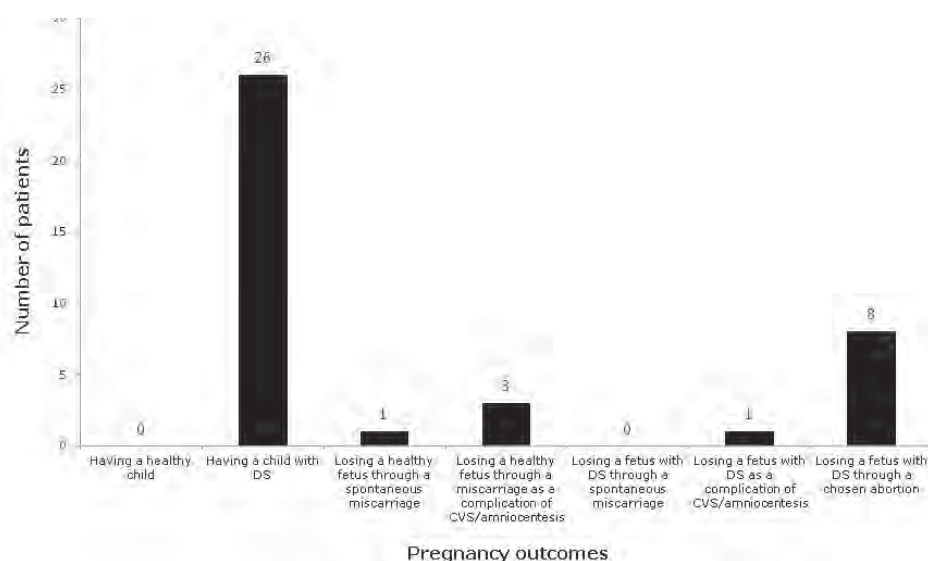


Fig. 8. Number of patients who responded to the question on the “Least desired pregnancy outcomes”.

for Down syndrome, the cut-off value that would indicate a high-risk FTS, and the procedure of invasive diagnostic tests with its associated risks. Having undergone these sessions, the majority of our patients were able to identify maternal age as a risk factor for Down syndrome, and 66% of the patients surveyed were able to recall KKH's cut-off for high-risk in the FTS test. Nevertheless, certain gaps in knowledge of our patients regarding Down syndrome still exist. A total of 34 patients (68%) had the incorrect impression that a high-risk value equated to the fetus either having Down syndrome most or all of the time. These gaps in knowledge and understanding of the FTS test may affect patients' ability to make informed decisions regarding FTS and invasive testing, and these gaps need to be bridged in order to achieve true informed decision-making.

We also saw from the survey that patients' preferences with regards to the type of FTS test they would choose to undergo vary from individual to individual. Most of the patients felt that highest accuracy was of highest priority

in a FTS screening test, followed by lowest false-positive rate, timing of the test and lastly cost of the test. In other simple preference studies, women report preferring an earlier over a later test, mainly because of the easier termination of pregnancy and/or the earlier reassurance provided.⁸ In more recent times, the advent of non-invasive prenatal testing for trisomy 21, 18 and 13 using cell-free DNA (cfDNA), whilst understanding its inherent limitations, is possibly a step towards providing a test with a higher sensitivity and lower false-positive rate.⁹ Nonetheless, this study and most other studies have shown that it is difficult to generalise each patient's preference with regards to choice of a screening test. Information for consideration of a choice (consent process) should thus include descriptions of different types of tests available and the benefits and disadvantages of each of them, such that patients can make decisions based on what they consider to be important to their circumstances and context. Otherwise, if the availability of the different choices of screening tests (that are supported by adequate

evidence) or important information regarding these tests is withheld from the patient, and the eventual decision of the patient conflicts with their personal values as a result of the omission, it could be considered unethical behaviour on the part of the medical practitioner.¹⁰

We see in our study that patients' perception of risk may not reflect the reported risk. This was observed in a study by Georgsson et al¹¹ in 2009 and is reflected in our study, where a number of women were concerned even at low-risk values of 1:500 and 1:1000. This may either be a reflection of the poor understanding of risk values or an inherent higher risk aversion in some patients as a result of them coming to screening with different backgrounds and life experiences, which impact on their decision-making processes. This highlights that doctors' perception of high- and low-risk does not automatically equate to patients' perception of risk, therefore when counselling patients, we need to take into consideration that even low-risk values may lead to patient anxiety and concerns.

Our study also showed how patients' perception of risk of Down syndrome does parallel with their willingness to undergo invasive testing procedures (Fig. 6). These results are consistent with a previous study published by Nicolaides et al¹² in 2005, which examined whether pregnant women were able to incorporate sophisticated screening information about risk assessment into their decisions about invasive testing in an appropriate way. In Nicolaides' study, it was seen that the rate of invasive testing increased exponentially with increasing estimated risk, and this observation was noted to be significant. However, in a retrospective study by O'Connell et al,¹³ 15% of women who had a positive test did not agree with the cut-off of 1:250 and declined invasive testing, while 0.08% of women with a negative triple test result requested for amniocentesis. This is similarly observed in our study, where women indicating concern about a given risk figure did not automatically commensurate with a decision to undergo invasive testing. This again may be due to different degrees of risk aversion and differing acceptability of various pregnancy outcomes. When faced with a high-risk screening result, discussion with the patient should consider her risk aversion to invasive testing and the values she attaches to different pregnancy outcomes to help decide on the next course of action.

Patients also have very different views on various pregnancy outcomes. Eight patients ranked having a chosen abortion for a fetus with Down Syndrome as the least desired pregnancy outcome of the given options, and 12 patients ranked having a child with Down syndrome as more acceptable than losing a healthy fetus through a miscarriage as a complication of CVS or amniocentesis. This highlights to us that different women view various pregnancy outcomes differently. Thus, after receiving an increased

screening result, obstetricians need to convey the message that invasive testing is not a self-evident step for them to take, but rather, an informed decision regarding invasive testing should be made based on the values an individual woman attaches to the possible pregnancy outcomes.

Strengths and Limitations

One of the strengths of our study was the providence of purpose-trained Malay and Chinese-speaking interviewers for patients who were not fluent in English, allowing the inclusion of as many women as possible to reduce selection bias. Patients were also allowed to clarify uncertainties regarding the questions with the interviewers, such that their answers would most reflect their true values and preferences. The inclusion of pictorial representations of risk rather than solely a numerical risk value helped to maximise their understanding of risk by focusing on the numerator (number of affected women) versus the denominator (number of unaffected women).

Currently, a validated questionnaire for risk perception in FTS does not exist. As such, one limitation of the study was that questions had to be created to assess risk perception with regards to FTS. In addition, this study was based on a relatively small sample size of 50 women, and thus, it cannot be generalised to depict all women choosing to undergo FTS. Also, the results should be viewed in a local context.

Conclusion

Aneuploidy screening is widely practiced in the field of obstetrics in current times. As such, examining the impact of this hitherto lesser considered aspect (autonomy) of screening on our patients is of substantial importance. This study demonstrates the diversity of pregnant women's risk perception, preferences, risk aversion and participation in decision processes when there are 2 different values in competition. The study also highlights our patients' gaps in knowledge and lack of understanding of risk values used in FTS. More needs to be done in the form of educating our population to address and bridge these gaps before a patient can truly exercise her autonomy to make informed decisions for her own pregnancy.

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Risk Factors for Severe Adenovirus Infection in Children during an Outbreak in Singapore

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Abstract

Background: Human adenoviruses (HAdVs) can cause a variety of human illnesses, with associated temporal and geographic changes in disease incidence. We report the emergence of an outbreak of HAdV infections in Singapore, presumably caused by a change of the predominating type to HAdV-7. We examined the clinical features of children admitted with HAdV infection to 1 institution and the risk factors for severe infection. **Materials and Methods:** This is a retrospective case-control study of all HAdV-infected children admitted during weeks 1 to 19 in 2013, as identified from laboratory records. A descriptive retrospective analysis of epidemiology, clinical data and the outcome of these children was also performed. Patients with severe infections were defined as cases, those with non-severe infections as controls, and the 2 groups were compared to find possible independent risk factors. **Results:** Eighty-five patients with HAdV infection were studied, including 11 (12.9%) cases and 74 (87.1%) controls. Binary logistic regression showed that cases were more likely to be <2 years old (adjusted OR 10.6, 95% CI, 1.8 to 63.2) and to have significant comorbidities (adjusted OR 19.9, 95% CI, 3.4 to 116.1) compared to controls. The predominant type in 2013 was HAdV-7, which differed from 2011 and 2012, when HAdV-3 was more common. There was a trend towards pneumonia being more common in patients infected with HAdV-7 than in patients infected with other types, although this did not reach statistical significance (OR 2.8, 95% CI, 0.9 to 8.7). **Conclusion:** The emergence of HAdV-7 in a population where other HAdV types had circulated previously may have caused the outbreak in Singapore, and this was associated with more serious infections in children. Young age (<2 years) and significant comorbidities were associated with more severe HAdV infection.

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Key words: Comorbidity, Complications, Epidemiology, Immunocompromised, Paediatric

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Introduction

Human adenoviruses (HAdVs) are well known pathogens that cause a variety of human illnesses. They are non-enveloped, linear double-stranded deoxyribonucleic acid (DNA) viruses. More than 50 distinct serotypes have been identified since the early 1950s. The wide spectrum of symptoms includes upper respiratory tract illness, pneumonia, conjunctivitis, cystitis and gastroenteritis.^{1,2} Characteristic illnesses associated with HAdVs are pharyngoconjunctival fever, epidemic keratoconjunctivitis and acute respiratory illnesses in military recruits. Immunocompromised persons are known to be affected by more severe disease.^{3,4} The

virus spreads rapidly in crowded environments, typically causing epidemics in military recruits and hospitalised or institutionalised civilians.^{5,6} In the paediatric population, particularly in children with underlying respiratory disease, the illness can be severe and life-threatening.⁷ Due to a large proportion of infections being subclinical and due to a lack of surveillance for HAdV infections in many countries, most community outbreaks remain unreported. A community outbreak of adenovirus was reported in Taiwan in 2011, using a vigilant surveillance system comprising 12 contract virological laboratories across the country.⁸

We noticed an apparent increase in the incidence of HAdV

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infections at our institution, a tertiary-care paediatric hospital in Singapore, KK Women's and Children's Hospital (KKH), during the first half of 2013. This was based on an increase of HAdV-positive specimens identified via microbiology laboratory records, and an apparent increase of patients requiring hospital admission, including patients with severe disease. In the present article, we report some of the characteristics of this outbreak and provide an analysis of the clinical features and risk factors associated with severe HAdV infections in children.

Methods

We conducted a retrospective case-control study combined with a descriptive analysis of epidemiology, clinical data and outcome among children with HAdV infections admitted to our tertiary-care paediatric hospital in Singapore. The HAdV-positive patients were identified from microbiology laboratory records over the period from 1 January 2013 to 13 May 2013 (weeks 1 to 19 in 2013). Children between the ages of 1 month and 17 years were included in the study. Factors such as demographics, clinical presentation, severity of illness, complications and management were recorded. For the purpose of the case-control study, HAdV-positive subjects, whose severity of illness required admission to the high dependency (HD) unit or the children's intensive care unit (CICU) were defined as 'cases'. The remaining HAdV-positive subjects, who did not require HD or CICU admission, were classified as 'controls'. Admission to the HD unit or the CICU was based on clinical judgment by the attending physicians, in combination with respiratory, circulatory or mental state parameters that were indicative of severe illness. Respiratory distress, including the requirement for supported ventilation, was the commonest reason for escalation of care to the HD unit or CICU. Others included a requirement for circulatory support or close monitoring for changes in mental status.

Based on clinical presentation, testing for HAdV was done on relevant samples using the following methods: (a) specific (genus-wide) HAdV real-time polymerase chain reaction (PCR), based on an assay by Heim et al;⁹ (b) respiratory virus direct immunofluorescence (IF) test (D3 Double Duet™ DFA Respiratory Virus Screening & ID Kit, Diagnostic Hybrids, Athens, OH, USA); and (c) respiratory virus multiplex PCR (Seeplex RV15 ACE Detection Kit, Seegene, Seoul, Korea). Positive samples were forwarded to the Singapore National Public Health Laboratory (NPHL) for further analysis, including virus culture (when feasible) and genotyping. HAdV genotyping was performed using a method developed by Lu and Erdman,¹⁰ by sequence comparison of a ~750 bp segment containing hexon gene hypervariable regions 1-6 (HVR 1-6). Data on HAdV types were then compared with other

clinical and epidemiological data.

The virus panel in the routine IF test consisted of influenza A and B viruses, HAdV, parainfluenza 1, 2 and 3 viruses, respiratory syncytial virus and metapneumovirus, and the multiplex PCR panel contained, in addition, parainfluenza 4 virus, human coronaviruses 229E, NL63 and OC43, enterovirus and bocavirus. It is common hospital practice at KKH to request the IF panel for most respiratory tract infections in children, while the multiplex PCR panel is usually requested for more difficult or severe cases. In addition, routine bacteriology tests are requested based on clinical indication.

Statistical analysis was performed using the SPSS statistical software programme, version 19 (IBM Corporation, Armonk, NY, USA). The chi-square tests and Fisher's exact tests were used for categorical data, and the t-test and Mann-Whitney U test for continuous data. Binary logistic regression analysis was used to examine risk factors that were significant in the univariate analysis. Forward stepwise regression was used for identifying the optimum variables for the model. This study was approved by the Singhealth institutional review board and approval was obtained for a waiver of patient consent.

Results

Epidemiology

From week 1 to 19 of 2013, 85 patients admitted to KKH had positive test results for HAdV. Eleven patients (12.9%) had severe infections, required admission to HD or CICU, and were defined as cases, and 74 children (87.1%) had non-severe infections, did not require admission to HD or CICU and were defined as controls.

Among the 85 HAdV-positive patients, 64 (75.3%) had HAdV detected by IF, and 21 (24.7%) had HAdV detected by PCR in nasopharyngeal swabs. Twenty of the 21 PCR-positive patients had initially been negative by IF testing and were subsequently tested by PCR, in view of a strong clinical suspicion of HAdV infection. Three out of the 85 patients had HAdV detected from additional sites. One patient (designated Patient A) had positive PCR results from blood, stool and a colon biopsy (post bone marrow transplant with adenovirus infection causing colitis), 1 patient had a positive HAdV PCR result from urine, and 1 patient (designated Patient B) with acute respiratory distress syndrome (ARDS) had a positive HAdV PCR result from a bronchoalveolar lavage specimen.

Demographics and Underlying Comorbidities

The median age of our patients was 34 months, with a mean age of 48.6 months (range, 3 to 187 months), and 53 (62.4%) were males. The ethnicities of the patients were

Chinese (42.4%), Malay (41.2%), Indian (12.9%), and others (3.5%). Fourteen patients (16.5%) had significant underlying comorbidities, such as cardiopulmonary diseases that included tracheobronchomalacia and pulmonary hemosiderosis (8.2%), neurological diseases that included methyl-CpG-binding protein 2 (*MECP2*) duplication syndrome and spastic quadriplegic cerebral palsy (4.7%), immunodeficiency, consisting of X-linked chronic granulomatous disease (2.4%), and haemato-oncological diseases, consisting of chronic idiopathic thrombocytopenic purpura (1.2%).

Clinical and Laboratory Characteristics

Clinical characteristics of the HAdV-positive patients are shown in Table 1. All cases were examined by a senior doctor in paediatrics (rank of paediatric registrar and above). The most common symptoms were fever (97.6%), cough (80%) and coryza (76.5%). Conjunctivitis was present in 18 patients (21.2%). The mean duration of fever was 7.4 days (range, 0 to 20 days). Physical examination findings included lung crepitations (12.9%) and rhonchi (11.8%). The most common HAdV-related presentations were upper respiratory tract infection (55.3%), pneumonia (22.4%), gastroenteritis (7.1%) and tonsillitis (7.1%). Severe disease complications included pleural effusion (4.7%), with half of them (2/4, 2.4%) requiring chest tube drainage, acute respiratory distress syndrome (ARDS; 2.4%), disseminated intravascular coagulopathy (DVC; 3.5%), seizures (3.5%) and encephalopathy (2.4%). A total of 54 of 85 (63.5%) patients had at least 1 complication (a list of complications is provided in the section 'Comparison between cases and controls').

Laboratory investigations are shown in Table 2 which includes a comparison between cases and controls. Statistical

Table 1. Clinical Characteristics of HAdV-positive Patients (n = 85)

Characteristics	Number of Patients (%)
Symptoms	
Fever	83 (97.6)
Conjunctivitis	18 (21.2)
Rash	8 (9.4)
Cough	68 (80.0)
Coryza	65 (76.5)
Sore throat	11 (12.9)
Diarrhoea	25 (29.4)
Vomiting	30 (35.3)
Abdominal pain	12 (14.1)
Signs	
Lung crepitations	11 (12.9)
Lung rhonchi	10 (11.8)
Stridor	1 (1.2)
Hepatomegaly	3 (3.5)
Splenomegaly	2 (2.4)
Lymphadenopathy	2 (2.4)

HAdV: Human adenovirus

significance analysis (Mann-Whitney U test) was not done for results that had a skewed distribution due to a wide range of normal values. When clinically indicated, further microbiological testing was done for bacterial and other viral pathogens. Coinfections with other presumptive pathogens were seen in 12 of 85 (14.1%) patients (Table 3). Viral coinfections were detected in 5 patients (5.9%) and included bocavirus, rhinovirus, parainfluenza virus and enterovirus. Six patients (7.1%) had concurrent bacterial infection or colonisation with potential pathogens, and 1 patient had coinfection with fungi.

Table 2. Laboratory Investigations Done in HAdV-positive Patients, with a Comparison between Cases and Controls

Laboratory Results (Median Values) and Number of Patients Tested	All	Cases	Controls	P Value
Haemoglobin, g/dL (range), n = 80	11.6	8.7 (6.8 – 11.4)	11.7 (8.9 – 15.4)	<0.0001
Leukocytes, $\times 10^3$ cells/ μ L (range), n = 80	11.5	5.6 (1.4 – 46.6)	11.5 (3.2 – 32.6)	0.279 (NS)
Neutrophils, $\times 10^3$ cells/ μ L (range), n = 80	6.1	3.3 (0.7 – 21.0)	6.2 (1.0 – 28.7)	0.137 (NS)
Lymphocytes, $\times 10^3$ cells/ μ L (range), n = 80	6.1	1.2 (0.1 – 1.6)	2.8 (0.9 – 12.1)	<0.0001
Platelets, $\times 10^3$ / μ L (range), n = 80	233	132 (29 – 376)	241 (35 – 575)	0.046
Urea, mg/dL (range), n = 58	3.0	4.1 (2.7 – 26.6)	2.8 (1.3 – 6.4)	0.001
Creatinine, μ mol/L (range), n = 58	43	46 (38 – 209)	43 (32 – 67)	0.204 (NS)
Sodium, mmol/L (range), n = 58	136	134 (131 – 140)	137 (131 – 140)	*
ALT, IU/L (range), n = 22	16	41 (10 – 1033)	15 (8 – 76)	*
AST, IU/L (range), n = 22	32	43 (17 – 1374)	28 (15 – 78)	*
CRP, mg/dL (range), n = 48	35.8	45.7 (7.2 – 348.7)	34.8 (0.7 – 185.4)	*

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; HAdV: Human adenovirus; NS: Not significant.

*Statistical significance analysis (Mann-Whitney U test) was not done for results with skewed distribution due to wide range of normal values.

Table 3. Coinfecting Pathogens in HAdV-positive Patients

Organisms Identified	Number of Patients (%)
Viral	5 (5.9)
Bocavirus	1 (1.2)
Bocavirus, parainfluenza 1 virus	1 (1.2)
Enterovirus	1 (1.2)
Metapneumovirus	1 (1.2)
Rhinovirus	1 (1.2)
Bacteria	6 (7.1)
<i>Stenotrophomonas maltophilia</i> (ETTA)	2 (2.4)
<i>Acinetobacter baumannii</i> (tracheostomy aspirate)	1 (1.2)
<i>Escherichia coli</i> (urine)	1 (1.2)
<i>Moraxella catarrhalis</i> , <i>Klebsiella</i> species (ETTA)	1 (1.2)*
<i>Haemophilus influenzae</i> (ear and eye swab)	1 (1.2)*
<i>K. pneumoniae</i> (blood)	1 (1.2)
Fungi	1 (1.2)
<i>Candida albicans</i> , <i>C. dubliniensis</i> , <i>Aspergillus fumigatus</i> , <i>A. terreus</i> (BAL)	1 (1.2)†

BAL: Bronchoalveolar lavage; ETTA: Endotracheal tube aspirate; HAdV: Human adenovirus

*These coinfecting pathogens were isolated from different sample sites of the same patient.

†This patient with trisomy 21 and pulmonary haemosiderosis had 4 fungi in addition to adenovirus.

HAdV Typing

Adenovirus genotyping was successful in 76 (89.4%) samples (Table 4). Almost all HAdV isolates from KKH were genotyped in 2012 and 2013 but only 15% were genotyped in 2011. The majority of patients (44 out of 76 samples, 57.9%) were found to be infected with HAdV-7. This was in contrast to available paediatric genotyping data from

NPHL obtained in 2011 and 2012, where the predominant type was HAdV-3, and HAdV-7 accounted for none and only 9.7% respectively, of the total HAdV serotypes. A statistical comparison of HAdV-7 versus non-HAdV-7 types between the 2012 and 2013 study period showed a statistically significant shift towards HAdV-7 in 2013 (OR 12.8, 95% CI, 5.2 to 31.5). There was a trend towards pneumonia being more common in patients infected with HAdV-7 (15/44) than in patients infected with other types (5/32), although this did not reach statistical significance (OR 2.8, 95% CI, 0.9 to 8.7).

Management and Outcome

Intravenous hydration was required in 40% of patients in view of poor oral intake. Oxygen supplementation was necessary in 14.1% of patients, and 16.5% of the children also required bronchodilators. One of the 7 cases (designated Patient C) who required assisted ventilation received non-invasive ventilation, as the parents opted for non-escalation of care in view of poor premorbid status, and the patient eventually passed away from the illness. Another patient (designated Patient B) required extracorporeal membrane oxygenation (ECMO) for severe ARDS. She had underlying pulmonary hemosiderosis requiring long-term corticosteroids, trisomy 21, polyarticular juvenile idiopathic arthritis and hypothyroidism, and died from her illness.

Antibiotics were started empirically for clinically suspected pneumonia and given orally in 44.7% and parenterally in 35.3% of the patients. Intravenous cidofovir was given to 3 patients with severe illness, at the discretion of the attending paediatric infectious diseases specialist, at a dose of 5 mg/kg once a week, together with probenecid. However, 2 of these patients had severe disease with ARDS and eventually died. The third patient (Patient A) had colitis secondary to adenovirus infection on day 28 after bone marrow transplant. Cidofovir was given for 2 doses weekly and then discontinued after the patient's symptoms had

Table 4. Adenovirus Typing Results

Type	Cases (n = 11, %)	Controls (n = 65, %)	Odds Ratio (95% CI)	2013* (n = 76, %)	2012 (n = 72, %)	2011 (n = 47, %)†
1	0	1 (1.5)		1 (1.3)	9 (12.5)	10 (21.3)
2	0	2 (3.1)		2 (2.6)	5 (6.9)	6 (12.7)
3	1 (9.1)	6 (9.2)		7 (9.2)	24 (33.3)	25 (53.1)
4	2 (18.2)	19 (29.2)		21 (27.6)	16 (22.2)	2 (4.2)
5	0	1 (1.5)		1 (1.3)	5 (6.9)	0
7	8 (72.7)	36 (55.4)	2.1 (0.5 – 8.8)	44 (57.9)	7 (9.7)	0
8	0	0		0	2 (2.7)	4 (8.5)
Others (15, 19, 41)	0	0		0	4 (5.5)	0

*The 2013 HAdV typing data is for the study period Jan-May 2013.

†Only 15% of HAdV isolates from KKH were typed in 2011, whereas almost all isolates were typed in 2012 and 2013.

improved. The mortality rate for the entire cohort of patients with HAdV infection was 3.5% (3 deaths). This included the 2 patients previously mentioned (Patient B and Patient C) and another one who had spastic quadriplegic cerebral palsy and was dependent in all activities of daily living.

On discharge, 1 patient who was previously well, had neurological sequelae of oropharyngeal dysphagia requiring nasogastric tube feeding. One patient had respiratory sequelae and was discharged on continuous positive airway pressure (CPAP) ventilation with oxygen. This patient had a history of *MECP2* duplication syndrome with global developmental delay but had been able to breathe in ambient air before his admission with HAdV infection.

Comparison between Cases and Controls

Table 5 shows an analysis to compare demographics, disease presentation, complications and treatment of cases ($n = 11$) with controls ($n = 74$). There was no statistical difference between the gender of the cases and controls. Although our study population included a higher proportion of patients of Malay ethnicity compared to the general population of Singapore (13.3% in 2013), there was no statistical difference in ethnicity between of the cases and controls. Cases were more likely to be <2 years old compared to controls (Pearson chi-square $P = 0.003$, OR 7.2, 95% CI, 1.7 to 29.9). Significant comorbidities were more likely to be seen in cases than controls (OR 16.8, 95% CI, 3.9 to 71.7). Binary logistic regression (using the variables significant in univariate analysis) confirmed the above findings, that cases were more likely to be <2 years (adjusted OR 10.6, 95% CI, 1.8 to 63.2) and to have significant comorbidities (adjusted OR 19.9, 95% CI, 3.4 to 116.1) compared to controls. Patients presenting with pneumonia were more likely to be complicated cases compared to those presenting with upper respiratory tract infection (URTI), bronchiolitis, bronchitis or tonsillitis ($P < 0.0001$).

Renal impairment, significantly elevated transaminases and haematological changes including lymphopenia, thrombocytopenia and anaemia were more likely to be present in cases rather than controls. The other obvious finding expected from the classification applied, was that, complications such as DIVC, pleural effusion requiring drainage, ARDS requiring invasive ventilatory support or ECMO, and hypotension requiring inotropic support, occurred significantly more frequently in cases compared to controls. Viral coinfections were more likely to be seen in cases than in controls (3/11 in cases and 2/74 in controls; $P = 0.001$). Similarly, concurrent bacterial infection or colonisation with potential pathogens were also more likely to be present in cases (4/11 in cases and 2/74 in controls; $P < 0.0001$).

Among those patients for whom HAdV genotyping was available, type 7 was found more commonly in cases (8/11, 72.7%) compared to controls (36/65, 55.4%), but the difference was not statistically significant (OR 2.1, 95% CI, 0.5 to 8.8). Of the 3 patients who died, 2 were infected with HAdV-7 and 1 with HAdV-4.

Discussion

This article describes an apparent increase in the numbers of admissions of patients with HAdV infections to a tertiary-care children's hospital in Singapore. Figure 1 depicts the trend in the numbers of HAdV positive paediatric samples in our institution during the preceding 10 years, as determined by IF testing. Prior to 2013, on average, the numbers of HAdV-positive samples per month were less than 5 to 10 during non-peak periods and up to about 15 to 25 during peak periods. The different peak and non-peak periods presumably reflect fluctuations of virus activity in the community over the 10-year period. The study period in the first half of the year 2013 stands out, with peaks of 25 positive samples in each, March and April, and 42 in May. The total numbers of samples submitted for IF testing (Fig. 1) increased over the years and a direct comparison between 2013 and earlier years from 2003 to 2009 is difficult due to smaller numbers of samples submitted for testing in those years. Nevertheless, the number of samples tested for HAdV plateaued from 2010 onwards and remained nearly unchanged. The hospital's HAdV sampling and testing practices by IF also remained unchanged during the 10-year period. This suggests that there was a distinct change in HAdV epidemiology in 2013, perhaps similar to a smaller peak period in 2011, that led to an increase of patients with HAdV infection seen at our hospital (Fig. 1).

During the study period, the clinical course of the admitted patients showed a substantial proportion of clinical complications (63.5%) and mortality (3.5%). A recent study from China identified HAdV as a cause in 9.6% (13 out of 136 respiratory pathogens identified in 105 patients) of acute respiratory infections (ARI), and the majority occurred in children under the age of 6 years (11/13).¹¹ This is in keeping with a previous study that showed HAdV to be involved in 5% to 10% of ARIs in children, and to be commonly occurring together with other viruses.¹² Coinfections with viruses occurred in 5.9%, and concurrent bacterial infection or colonisation in 7.1% of our patients.

In our study, HAdV illness tended to be more severe in children less than 2 years of age. Previous reports looking at risk factors for severe HAdV infections do not clearly show young age as a risk factor for severe illness.⁸ On the other hand, it is well documented that children with underlying neurological, metabolic or respiratory conditions

Table 5. Univariate Comparison of Cases and Controls

Characteristic	Cases (n = 11)	Controls (n = 74)	Odds Ratio (95% CI)
Age (years)			
Mean	2.6	4.3	
Median	1.4	3.2	
Range	8 months to 13.7 years	3 months to 15.6 years	
Age group, n			
<2 years	8	20	7.2 (1.7 – 29.9)
≥2 years	3	54	
Male, n (%)	6 (54.5)	47 (63.5)	1.1 (0.3 – 4.3)
Ethnicity, n (%)			
Chinese	4 (36.4)	32 (43.2)	
Malay	4 (36.4)	31 (41.9)	
Indian	3 (27.3)	8 (10.8)	
Others	0	3 (4.1)	
Significant comorbidities			
Immunodeficiency	1	1	
Neurological	4	0	
Cardiopulmonary	2	5	
Haematological	0	1	
Total, n (%)	7 (63.6)	7 (9.5)	16.8 (3.9 – 71.7)
Disease presentation, n (%)			
Pneumonia	9 (81.8)	10 (13.5)	
URTI	0	47 (63.5)	
Gastroenteritis	0	6 (8.1)	
Bronchiolitis/bronchitis	0	3 (4.1)	
Tonsillitis	0	6 (8.1)	
Haemorrhagic cystitis	0	1 (1.4)	
Encephalopathy	0	1 (1.4)	
Pneumonia with Encephalopathy	1 (9.1)	0	
Colitis	1 (9.1)	0	
Complications, n (%)			
Pleural effusion (conservative treatment)	1 (9.0)	1 (1.4)	7.3 (0.4 – 126.1)
Pleural effusion (requiring drainage)	2 (18.2)	0	
ARDS	2 (18.2)	0	
DIVC	3 (27.3)	0	
Encephalopathy	1 (9.0)	1 (1.4)	7.3 (0.4 – 126.1)
Seizures	2 (18.2)	1 (1.4)	16.2 (1.3 – 197.3)
Renal impairment	3	0	
Elevated transaminase ALT >2x normal	5 (n = 7)	2 (n = 15)	16.3 (1.8 – 148.8)
Elevated transaminase ALT >2x normal	5 (n = 7)	2 (n = 15)	16.3 (1.8 – 148.8)

ALT: Alanine aminotransferase; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase; DIVC: Disseminated intravascular coagulopathy; NS: Not significant; URTI: Upper respiratory tract infection

*Haemoglobin <10 g/dL

†Leukocyte count <5000 cells/μL

‡Neutrophil count <1000 cells/μL

§Lymphocyte count <1000 cells/μL

||Platelet count <150,000/μL

Table 5. Univariate Comparison of Cases and Controls (Con't)

Characteristic	Cases (n = 11)	Controls (n = 74)	Odds Ratio (95% CI)
Anemia*	8 (n = 11)	4 (n = 69)	43.3 (8.2 – 229.6)
Leukopenia†	7 (n = 11)	2 (n = 69)	19.1 (3.0 – 123.9)
Neutropenia‡	1 (n = 11)	1 (n = 69)	6.8 (0.4 – 117.6)
Lymphopenia§	4 (n = 11)	4 (n = 69)	9.3 (1.9 – 45.5)
Thrombocytopenia	5 (n = 11)	5 (n = 69)	10.7 (2.4 – 47.6)
Treatment given, n (%)			
Oxygen	9 (81.2)	3 (4.1)	106.5 (15.6 – 725.6)
Bronchodilators	9 (81.2)	5 (6.8)	62.1 (10.5 – 368.6)
Intravenous cidofovir	3 (27.3)	0	

ALT: Alanine aminotransferase; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase; DIVC: Disseminated intravascular coagulopathy; NS: Not significant; URTI: Upper respiratory tract infection

*Haemoglobin <10 g/dL

†Leukocyte count <5000 cells/ μ L

‡Neutrophil count <1000 cells/ μ L

§Lymphocyte count <1000 cells/ μ L

||Platelet count <150,000/ μ L

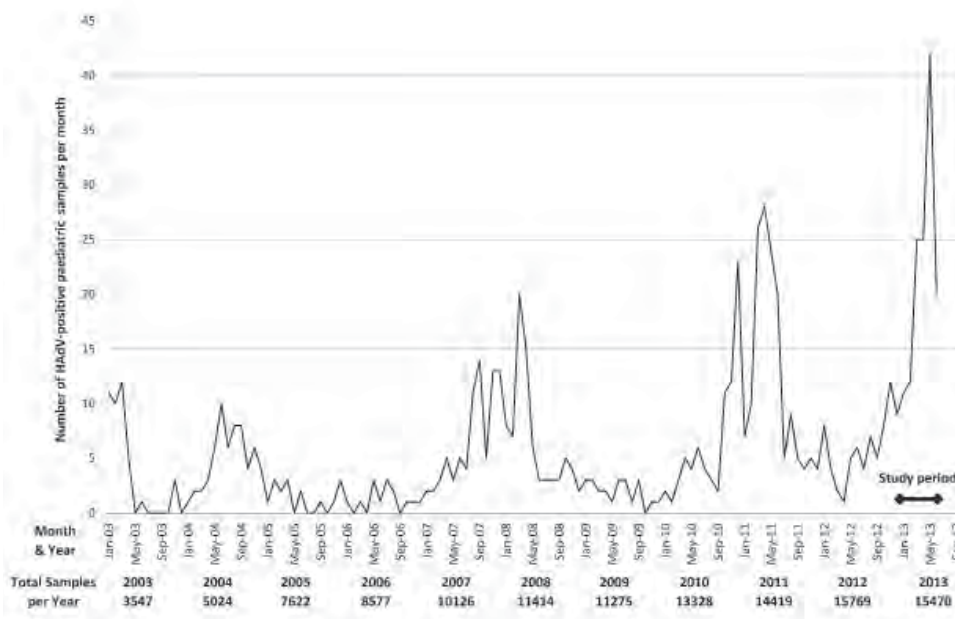


Fig.1. Trend of HAdV-positive paediatric specimens over 10 years, between January 2003 and June 2013. The figure shows the absolute numbers of HAdV-positive specimens per month, as determined by the respiratory virus direct immunofluorescence test. The period of the present report (January 2003 to May 2013) is indicated. The total numbers of samples submitted each year for IF testing is also shown along the X axis for reference.

are more likely to develop more severe illness.¹³⁻¹⁶ In addition to neurological or pulmonary disease, children with other comorbidities, including immunodeficiency and cardiopulmonary disease, were also more likely to have severe disease in our study. The complications of pleural effusion and haematological cytopenias found in severe infections (cases) were comparable to those found in a similar study in Taiwan in 2011.⁸ We further report 2 severe cases with ARDS, one of these requiring ECMO, and both patients eventually passed away despite cidofovir treatment. A third death occurred in a child with

an underlying neurological condition (Patient C). Severe illness was, however, also observed in 4 previously healthy children with no relevant pre-existing comorbidities.

The role of HAdV in the aetiology of severe acute respiratory illnesses in immunocompromised patients is well documented.¹⁷ Depending on the immunosuppressive regimen, rates of HAdV infection of 2% to 21% with a mortality rate ranging from 10% to 60% have been described.¹⁸ Most HAdV infections, however, are mild, self-limiting illnesses. Different serotypes are associated with different clinical manifestations by virtue of variable tissue

tropism. *HAdV-3* has been identified in several outbreaks across different continents over the years.¹⁹ Greater severity of this generally benign *HAdV-3* serotype has been reported in a paediatric long-term facility outbreak in Illinois in 2005, associated with substantial morbidity and mortality in children with underlying respiratory conditions.²⁰ Several adenovirus outbreaks have been reported in Asia. Notable ones have been reported from Taiwan; this includes one between 1999 and 2001, involving serotypes *HAdV-3*, -7 and -4,²¹ another in 2004 to 2005 with *HAdV-3*,²² and more recently, an outbreak in 2011, with types 3 and 7 causing severe respiratory infections with respiratory failure in children.²³ Concurrent circulation of *HAdV-3* and *HAdV-7* during outbreaks has been reported in other populations.^{8,24}

HAdV-7 has previously been reported to be associated with severe clinical illness and morbidity.^{13,25,26} In China, *HAdV-7* contributed to an outbreak of pneumonia in infants in 2011²⁵ and was also reported to have a higher case fatality rate compared to *HAdV-3*.¹⁴ In a case cluster in California, *HAdV-7b* was involved in severe respiratory illness in children and associated with a high number of deaths; 4 out of 6 patients (66.6%) with *HAdV-7b* died of the infection.²⁷ Another outbreak of *HAdV-7* infection, causing life-threatening disease, was reported in an institution for disabled children.¹³ A high case-fatality rate with *HAdV-7* was also reported from Taiwan in 2010 to 2011. Among severe cases requiring intensive care, the mortality rate for serotype 7 was 32%, compared to 14% for non-serotype 7 infections.²³ Although different *HAdV-7* subtypes have been reported in various parts of the world to be associated with outbreaks and severe clinical infections,²⁸⁻³¹ a serotype prevalence and risk factor study in USA in 2004 to 2006 did not show a strong association of *HAdV-7* with severity of infection.¹⁵ Therefore, there seems to be conflicting evidence for the association of *HAdV-7* with severe clinical disease.

Our experience in the paediatric population in Singapore in previous years showed *HAdV-3* to be the predominant serotype among the isolates that were typed (33.3% in 2012 and 53.1% in 2011). *HAdV-7* was not isolated in any of the samples serotyped in 2011. There were less *HAdV-7* among the samples in 2012 (9.7%, 7/72) compared to the high number (51.8%, 44/76) in 2013, thus showing the emergence of a different predominant serotype causing respiratory illness among hospitalised children. Strict infection control measures were employed to prevent nosocomial spread of HAdV in our hospital.

Treatment of HAdV infections has not been well studied; in particular, information from well designed clinical trials is lacking, but from the available information, cidofovir is considered the drug of choice for severe HAdV infections.³² In immunocompromised patients, especially in the scenario after stem cell transplant, where reactivation and horizontal

transmission may cause severe and life threatening illness,³³ cidofovir is the most accepted antiviral therapy.³⁴ Three of our 11 patients (27.3%) with severe HAdV disease, who also had underlying comorbidities, were treated with cidofovir, 2 of whom (including patient B) died of adenovirus-associated ARDS. The decision to treat with cidofovir was at the discretion of the infectious diseases specialist, based on the severity of the illness and presence of underlying comorbidities. The third patient treated with cidofovir (Patient A) had colitis and survived. Of the 8 patients with severe HAdV disease who were not treated with cidofovir, 4 had comorbidities (ex-prematurity, neuroregressive disorder, *MECP2* duplication syndrome and tracheobronchomalacia). Of these, 3 recovered, and the patient with neuroregressive disorder (Patient C) died. In terms of preventative measures, vaccines would be a potentially attractive option, but the only formulation that is currently available is used solely for US military recruits for preventing acute respiratory disease.^{24,35} Currently, there is no HAdV vaccine available for use by the general public.

The main side effect limiting the use of cidofovir is nephrotoxicity. None of our 3 patients treated with intravenous cidofovir showed apparent drug-related side effects. Safety, efficacy and a better side-effect profile with lesser nephrotoxicity has been shown with the use of hexadecyloxypropyl cidofovir (CMX001), an orally bio-available lipid conjugate of cidofovir in a study of immunocompromised HAdV-infected patients.³⁶

Our study has 2 main limitations. First, the decision to admit patients to the HD unit or to the CICU—which determined whether a patient would be designated as a ‘case’ or a ‘control’—was based on a combination of clinical judgement, pathophysiological and laboratory parameters, mostly before HAdV test results were available. Thus, our classification as severe or non-severe, which formed the basis of our risk factor analysis, was not solely based on objective criteria, and this may have unknowingly influenced our analyses. Second, our cohort of 11 severe cases as well as our overall number of patients was relatively small, and this has had a limiting effect on the statistical power of our analyses. For example, it is possible that the comparison of pneumonia cases caused by *HAdV-7* versus the other types would have reached statistical significance if the sample size had been bigger. Nevertheless, both limitations reflect ‘real-life’ conditions encountered during a HAdV outbreak at a single tertiary-care institution, and our observations add to the growing knowledge concerning the epidemiological and clinical features of HAdV infections.

Conclusion

HAdV infections can cause community outbreaks, and severe HAdV infections can be seen especially with *HAdV-*

7. In the present study, severe infection was found more frequently in patients <2 years old and those with underlying comorbidities. A change in serotype from *HAdV-3* in 2011 to *HAdV-7* in 2013 may have contributed to this outbreak in Singapore that resulted in an increase in *HAdV*-related paediatric admissions.

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Relationships between Prostatic Volume and Intravesical Prostatic Protrusion on Transabdominal Ultrasound and Benign Prostatic Obstruction in Patients with Lower Urinary Tract Symptoms

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Abstract

Introduction: The objective of this study is to determine the relationships between prostatic volume (PV) and intravesical prostatic protrusion (IPP) with benign prostatic obstruction (BPO). **Materials and Methods:** A total of 408 males (aged 50 years and above) who presented with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) were recruited. All had International Prostate Symptoms Score (IPSS), quality of life (QOL) index, uroflowmetry (Qmax) and postvoid residual urine (PVR) measured by transabdominal ultrasonography (TAUS). The PV and the degree of IPP were also measured by TAUS in the transverse and sagittal planes respectively. The PV is classified as Grade a, (20 ml or less), Grade b, (more than 20 ml to 40 ml) and Grade c, (more than 40 ml), while the IPP is graded as Grade 1 (5 mm or less), Grade 2 (more than 5 mm to 10 mm) and Grade 3 (more than 10 mm). **Results:** There was a fair positive correlation between the PV and IPP (Spearman, $r_s = 0.62$, $P < 0.001$) with important clinical exceptions. There was negative correlation between the PV and Qmax ($r_s = -0.20$, $P = 0.022$), IPP and Qmax ($r_s = -0.30$, $P < 0.001$). PV and IPP were good predictors of BPO. However, IPP was slightly better (r_s of -0.30 vs -0.20) than PV. **Conclusion:** PV is related to IPP with important clinical exceptions. IPP is a better predictor of BPO than PV.

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Key words: Benign prostatic hyperplasia, Prostate volume

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Introduction

Benign prostatic hyperplasia (BPH) is one of the commonest diseases of ageing men. It can be associated with bothersome lower urinary tract symptoms (LUTS) that affect quality of life and it causes structural and functional changes in the bladder. Previous clinical guidelines had emphasised on managing symptoms; however current thinking is that the prevention of progression of BPH is also important.¹ Progression depends not only on the size but also the shape of the prostate adenoma which causes obstruction, hence, the importance of studying the relationship between prostate volume (PV) and the intravesical prostatic protrusion (IPP). IPP which distorts the funneling effect of the bladder neck can be considered to represent the shape of the prostate. The severity of LUTS suggestive of BPH correlates poorly with benign prostatic obstruction (BPO).²⁻⁵ Differences in

the mean symptom index score in men with and without BPO were not statistically significant. Although pressure flow studies and voiding urethral pressure profilometry are reliable means of identifying BPO, they are not routinely performed for ageing men with LUTS suggestive of BPH. This is because urodynamic studies are acknowledged to be relatively complex, invasive and not cost-effective. The other non-invasive methods have not been effective for predicting BPO.⁶

The correlation of PV and BPO has been extensively investigated. It was generally accepted that there was weak correlation of PV with BPO. However, several recent studies indicated a stronger correlation between PV and BPO than previously reported.⁶⁻⁹ It had also been shown in our earlier study that the IPP was strongly correlated with BPO, 21% of the prostate with Grade 1 (defined by a IPP of equal or less

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than 5 mm) were obstructed, while for Grade 3 (defined by a IPP of more than 10 mm), 94% were obstructed on pressure flow study.¹⁰ Ochiai et al⁷ emphasised the importance of bladder weight and prostatic configuration in determining BPO, using transrectal ultrasound. Steele, Kuo and Ockrim et al^{6,8,9} used transrectal ultrasound to measure PV and configuration for predicting BPO. The transrectal approach is inconvenient and uncomfortable to patients. It may be unsuitable or unacceptable as an initial routine assessment tool to most patients.

Bedside ultrasound has been routinely used for evaluating the anatomical size (PV) and configuration (IPP) of the prostate gland and assessing postvoid residual urine (PVR) of patients with LUTS suggestive of BPH in our institution since 1997.¹⁰⁻¹⁵ In this study, we retrospectively investigated the relationship between PV and IPP and their relationship with BPO in patients who presented with LUTS.

Materials and Methods

Patients' Eligibility

An approval from the SingHealth Centralised Institutional Review Board was sought with a waiver of informed consent (CIRB Ref: 2012/311/D). A total of 408 consecutive male patients, aged 50 years and older who presented with LUTS suggestive of BPH between July 1997 and December 2003 were recruited in this study. Patients with a known history of previous lower urinary tract surgery, prostatic cancer, neurological disease such as cerebral vascular accidents and Parkinsonism were excluded.

Evaluations

The International Prostate Symptoms Score (IPSS) was used to assess the severity of LUTS and quality of life (QOL) index was used to evaluate if the symptoms were bothering the patients. Medical history taking and physical examination were performed. Digital rectal examination (DRE) was performed to exclude prostate cancer, and a neurological examination was performed to exclude neurogenic bladder dysfunction.

The patients were next assessed by bedside transabdominal ultrasonography (TAUS) with 3.5 MHz curvilinear probe (Ausonics Opus-257310). The PV was measured by TAUS in the transverse plane. It has been shown in our earlier study that TAUS measurement of PV correlated well with transrectal measurement when bladder volume is less than 400 ml.¹² The PV was classified as Grade a (20 ml or less), Grade b (more than 20 ml to 40 ml), and Grade c (more than 40 ml). The bladder capacity was approximately 150 ml to 250 ml before the extent of IPP was measured. The degree of IPP was graded by measuring the vertical distance from intravesical protruding prostatic tip to the imaginary bladder neck line in the midline sagittal plane.¹⁰⁻¹¹ The degree of IPP was classified as follows: Grade 1: 5 mm or less; Grade 2: more than 5 to 10 mm; Grade 3: more than 10 mm (Fig. 1).

After TAUS assessment, uroflowmetry was then performed to assess Qmax (peak flow rate). PVR was then measured by TAUS. To accurately measure PVR, repeated estimation of PVR was performed for patients

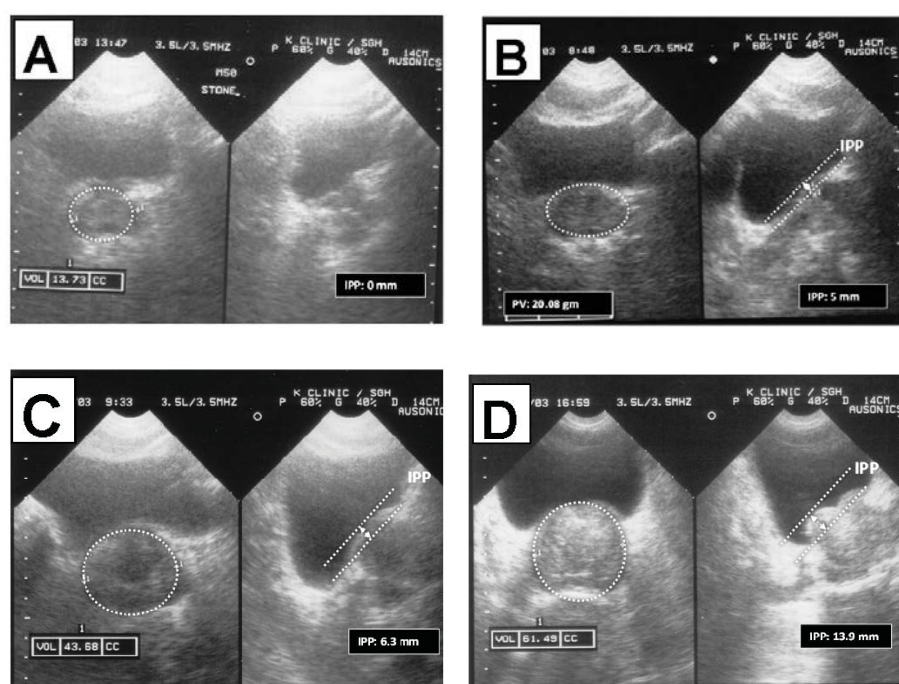


Fig 1. Grading according to intravesical prostatic protrusion (IPP). Slide A shows a normal prostate, slide B shows Grade 1, slide C shows Grade 2, and slide D shows Grade 3.

Table 1. The Baseline Clinical Characteristics (n = 408)

	Mean	Median	Standard Deviation	Minimum	Maximum
Age (years)	64	63	9	50	90
Prostate size (gm)	34	30	18	6	98
IPSS	12	10	7	0	34
QOL	3	3	1	0	6
Qmax (ml/sec)	12	11	5	1	41
PVR (ml)	54	34	69	5	1000

IPSS: International Prostate Symptoms Score; PVR: Postvoid residual urine; Qmax: Peak flow rate; QOL: Quality of life

Table 2. The Correlation of PV with Age, IPSS, IPP, Qmax, PVR, QOL (n = 408)

PV*	r_s	P Value
Age (years)	0.30	<0.001
IPSS	-0.03	0.612
IPP	0.62	<0.001
Qmax (ml/sec)	-0.20	0.022
PVR (ml)	0.16	0.004
QOL	0.08	0.157

*PV is related to age and IPP but not to IPSS and QOL

IPP: Intravesical prostatic protrusion; IPSS: International Prostate Symptoms Score; PV: Prostatic volume; PVR: postvoid residual urine; Qmax: peak flow rate; QOL: Quality of life

with abnormally high volume during the same visit or subsequent visit. Persistent PVR of 100 ml or greater would be suspected to be significantly obstructed.¹³ Also, we selected a cutoff value for urine flow rate of 10 ml/sec or below as a surrogate of obstruction.^{15,16}

Statistical Analysis

We used the SPSS 17.0 software for the statistical analysis. The Spearman correlation r_s , chi-square and one-way ANOVA tests were used as appropriate.

Results

The baseline clinical characteristics of this cohort (n = 408) are shown in Table 1. The correlations between total PV and age, IPSS, QOL, IPP, Qmax, and PVR are illustrated in Table 2. There was a weak correlation between PV and age ($r_s = 0.30$, $P < 0.001$), Qmax ($r_s = -0.20$, $P = 0.022$) and PVR ($r_s = 0.16$, $P = 0.004$). The scatterplot showed a linear regression between PV and IPP (Fig. 2). The correlation between PV and IPP was fairly strong ($r_s = 0.62$, $P < 0.001$). However, there was no significant correlation of PV with IPSS ($r_s = -0.03$, $P = 0.612$) and QOL ($r_s = 0.08$, $P = 0.157$).

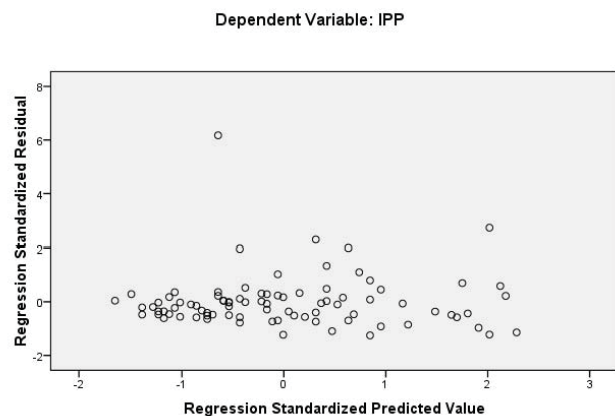


Fig. 2. Scatterplot showing the correlation between prostatic volume (PV) and intravesical prostatic protrusion (IPP).

The good relationship between PV and IPP can also be shown with chi-square tests ($\chi^2 = 129.212$, $P < 0.001$) (Fig. 3). The small prostate of 20 ml or less were mainly distributed in Grade 1, 20 ml to 40 ml prostate in Grade 2, >40 ml prostate in Grade 3.

The correlation of the combined classification PV with IPP (grade) and mean uroflow rate is shown in Table 3. The definition of BPH grade is a combination of the degree of IPP and the PV, e.g. Grade 1a corresponds to a patient with IPP of Grade 1 and a PV of Grade a. There were negative correlations between PV and average Qmax ($r_s = -0.20$, $P = 0.022$), IPP and average Qmax ($r_s = -0.30$, $P < 0.001$). One-way ANOVA test showed that mean Qmax was significantly lower for higher degree of IPP ($F = 18.075$, $P < 0.001$).

The correlation of BPH grade (combination of IPP and PV) and obstruction (defined as Qmax of 10 ml/sec and below) is shown in Figure 4. There was a significant negative correlation between BPH grade and the Qmax of 10 ml/sec and below (χ^2 for trend = 32.2, $P < 0.001$). Seventy-nine percent of patients with Grade 1a prostates had Qmax of over 10 ml/sec (not obstructed), and 64% of patients with Grade 3c prostates had Qmax equal or less than 10 ml/sec (obstructed). However, Grade 3a prostates of small size

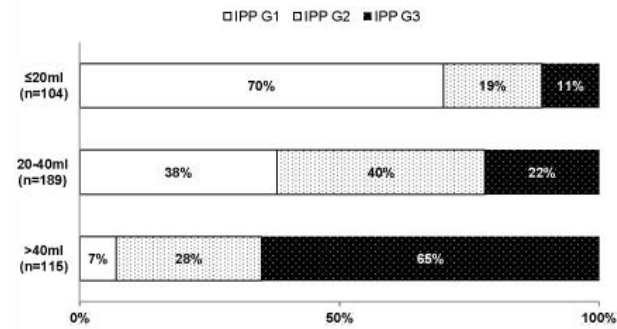


Fig 3. Bar chart showing the correlation between prostatic volume (PV) and intravesical prostatic protrusion (IPP), (n = 408). Note: IPP Grade 1: ≤5 mm; 2: >5 to 10 mm; 3: >10 mm. The percentages were the proportion of cases of each degree of IPP within each volume group (e.g. 73/104 = 70%).

but obvious IPP tended to be most obstructed at 82%. The Grade 1c prostates of large size but mild IPP prostate were rarely obstructed at 37%. Hence, IPP was a better predictor of bladder outlet obstruction (BOO) than PV.

Discussion

Using non-invasive evaluation techniques of TAUS and uroflowmetry, we evaluated correlation of PV, IPP and BPO. In our previous study, by using pressure flow studies, the results indicated that the IPP was a better and more reliable predictor of BPO than other variables.¹⁰ IPP was also a useful indicator for predicting the success of a voiding trial following acute urine retention (ARU).¹¹ In this study, our results further validated that IPP was indeed a better predictor of BPO. PV correlation with Qmax ($r_s = -0.20$, $P = 0.022$) is lower, compared to IPP correlation to Qmax ($r_s = -0.30$, $P < 0.001$). This study also showed that in

real life practice, any patient who presents with symptoms of BPH can be assigned a grade which is a combination of IPP (Grade 1, 2, 3) and PV (Grade a, b, c) (Fig. 1).

We found fairly strong correlation between PV and IPP ($r_s = 0.618$, $P < 0.001$) and a good consensus between PV and IPP. Seventy percent of patients with Grade 1 IPP had PV equal or less than 20 ml while 65% of patients with Grade 3 IPP had PV of more than 40 ml. There were, however, important exceptions. In our study, there were 11% (11/104) of patients with Grade 3 IPP having a PV of 20 ml or below, and 7% (8/115) of patients with Grade 1 IPP having PV of more than 40 ml (Table 3).

Using a cutoff value for Qmax ≤10 ml/sec as a surrogate for obstruction,¹⁵ our results showed significant negative correlation between various BPH grades (combination of IPP and PV), and obstruction ($\chi^2 = 43.101$, $P < 0.001$). In our study, we found that most of the patients with Grade 1a prostate were not obstructed (79%) (Qmax >10 ml/sec) while most patients with Grade 3c prostate were obstructed (64%) (Qmax ≤10 ml/sec). However, patients with Grade 3a prostate (small volume but obvious IPP) tend to be most obstructive with 82% having poor Qmax of equal or less than 10ml/sec. Patients with Grade 3a prostate had small total prostatic volume but had significant median lobe prostatic hyperplasia, resulting in ball-valve type of obstruction at bladder neck. On the other hand, patients with the Grade 1c prostate had large volume prostate but mild IPP were rarely obstructed; 63% of these patients had good uroflow with Qmax of more than 10ml/sec (Fig. 4).

Hence, our study once again showed a strong correlation between IPP and BPO. IPP is superior to PV in predicting BPO in patients who presented with LUTS. In our daily

Table 3. The Correlation of PV, IPP Grading with Average Qmax (n = 408)

No. of Cases (% of Total)	Grade*	Qmax (ml/sec)	Qmax Within Each IPP† Degree (ml/sec)	Total (%)
73 (18)	1a	14		
72 (18)	1b	13	14	153 (38)
8 (2.0)	1c	13		
20 (5)	2a	13		
75 (18)	2b	11	12	127 (31)
32 (8)	2c	11		
11 (3)	3a	8		
42 (10)	3b	11	10	128 (31)
75 (18)	3c	9		

IPP: Intravesical prostatic protrusion; PV: Prostatic volume; Qmax: Peak flow rate; QOL: Quality of life

*Grades 1, 2, 3 refer to the IPP grade: Grade 1: ≤5 mm; Grade 2: >5 to 10 mm; Grade 3: >10 mm. a,b,c refer to the size of the prostate: a: ≤20 grams; b: >20 to 40 grams; c: >40 grams. Thus Grade 1a refers to a prostate with IPP ≤5 mm with a size of ≤20 grams.

†Low IPP is associated with low PV 1a (18%). Moderate IPP is associated with moderate PV 2b (18%). High IPP is associated with large PV 3c (18%). However, there are exceptions with 2% in Grade 1c and 3% in Grade 3a. The higher the IPP, the lower the average Qmax.

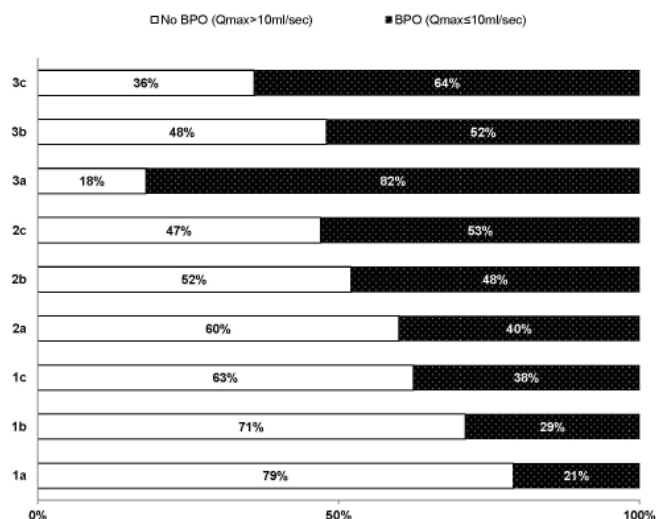


Fig 4. Bar chart showing the correlation between prostatic volume (PV) combined intravesical prostatic protrusion (IPP) and a cutoff value for peak flow rate (Qmax) of 10 or less ml/sec, n = 408. Note: BPO (benign prostatic obstruction) is defined as Qmax equal or less than 10ml/sec. Grade 3a is most obstructive and 1a is least obstructive. When IPP is 1 and 2, the degree of obstruction is related to the size. When IPP is Grade 3, then there is no correlation to the size, suggesting shape (IPP) is more important than size in causing obstruction.

clinical practice, we frequently encountered patients with large prostate volume who did not present with severe obstruction. Yet, some patients with small prostate volume can present with severe obstruction. Our results in this study will explain the reasons for that. Small prostate can have significant IPP due to median lobe hyperplasia, resulting in distortion of the funneling bladder neck, causing obstruction.

We have shown that IPP is also related to PV. IPP, with Qmax, helps to predict obstruction by BPH and therefore the progression of BPH (prostate adenoma) as well.¹⁷ IPP is useful in stratifying patients with LUTS at initial evaluation for further cost-effective management.

Our results would have important implications on patient management. Patients with Grade 3a prostate, being small, more obstructive would be better treated with surgery. While patients with Grade 1c prostate, being large and less obstructive, would be better treated medically with 5-alpha-reductase inhibitors (5-ARIs). Patients with Grade 3 IPP can confidently be diagnosed with obstruction before surgery. Only patients with low grade IPP, with poor flow, need further more invasive investigations such as pressure flow studies or flexible cystoscopy, if not responding to medical therapy and surgical treatment is contemplated.

The limitation of this study is the use of Qmax ≤ 10 ml/sec as a surrogate of obstruction. However, in clinical practice, it is not feasible to have pressure flow study on all our patients. It has been shown that 90% of patients with a

Qmax ≤ 10 ml/sec were obstructed on pressure flow study¹⁶ and this criterion is applied equally to IPP and PV in this analysis. Also, our previous study had already shown a strong co-relationship between IPP and BPO on pressure flow studies. The Spearman rho coefficient was 0.507 for IPP and 0.314 for PV. The receiver operator characteristic curve (ROC) for IPP was 0.77, compared to PV which was 0.637.¹⁸

Conclusion

We showed that PV and IPP are correlated with each other and with BPO, with important clinical exceptions. IPP is a better predictor of BPO than PV. IPP is easy to acquire and is non-invasive.

Acknowledgement

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Pharmacomechanical Thrombolysis versus Surgical Thrombectomy for the Treatment of Thrombosed Haemodialysis Grafts

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Abstract

Introduction: The key to treatment of a thrombosed dialysis graft is restoration and maintenance of function as long as possible. The objective of this study was to compare the outcomes of pharmacomechanical thrombolysis and surgical thrombectomy in the treatment of thrombosed haemodialysis grafts. **Materials and Methods:** During a 3-year period, 108 patients with 114 thrombosed dialysis grafts were referred to our institute for treatment. Fifty thrombosed dialysis grafts underwent pulse-spray catheter thrombolysis using recombinant tissue plasminogen activator (rt-PA) with angioplasty, and 64 thrombosed dialysis grafts underwent surgical thrombectomy. The procedural success rates, complications and average patency times and patency rates were compared between the 2 procedures. *P* values less than 0.05 were considered to be statistically significant. **Results:** There were no statistically significant differences between the pharmacomechanical thrombolysis group and the thrombectomy group in the procedural success rates (94% and 93.8%, *P* = 0.15) or average patency times (6.24 months and 6.30 months, *P* = 0.17). The primary and secondary patency rates at 12 months were 28.0% ± 8.4% and 54.3% ± 7.8% for the thrombolysis with angioplasty group, and 30.0% ± 6.3% and 57.0% ± 4.8% for the thrombectomy group, respectively (*P* = 0.65 and *P* = 0.49, respectively). There were no procedural-related major complications. **Conclusion:** Our study found no differences in outcomes between patients treated with pharmacomechanical thrombolysis and surgical thrombectomy for thrombosed haemodialysis grafts. Pharmacomechanical thrombolysis can be considered as an alternative treatment for dialysis graft thrombosis.

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Key words: Angioplasty, Arteriovenous graft, Thrombosis

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Introduction

Permanent dialysis vascular access is the primary route for haemodialysis in patients with chronic renal failure, usually through an arteriovenous fistula (AVF) or an arteriovenous graft (AVG). The AVF has many advantages over synthetic grafts, including better patency, lower rates of infection and a lower incidence of vascular steal syndrome; however, the major problems are immaturity or a prolonged time for maturity. Although the patency rate of the AVG is lower than the AVF, it is still more widely used because it is easier to create and can be used earlier than AVF for haemodialysis. A thrombosed haemodialysis vascular access occurs frequently in a prosthetic graft. Salvage of a thrombosed haemodialysis graft is essential to maintain haemodialysis and prolong the

quality of life. The traditional treatment of graft thrombosis is surgical thrombectomy with 1-year patency rates varying from 25% to 70%.¹⁻⁴ Currently, 2 percutaneous endovascular techniques are widely used for the treatment of thrombosed AVG, mechanical thrombectomy and pharmacomechanical thrombolysis. Mechanical thrombectomy is a procedure that uses a device for thrombus removal, which is faster than the pharmaceutical method. However, the thrombectomy device is expensive, and the procedure is not available in all institutions. Pharmacomechanical thrombolysis is a method to treat thrombosed haemodialysis grafts using a thrombolytic drug and balloon catheter. This method is easier to perform, and any experienced interventional radiologist can perform it. Several studies have reported

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1-year patency rates of 57% to 69% with this method.⁵⁻⁹

Pharmacomechanical thrombolysis for the treatment of thrombosed haemodialysis graft has been performed in our institute since 2009. The purpose of this study was to report our experience with pharmacomechanical thrombolysis compared with surgical thrombectomy in thrombosed haemodialysis grafts.

Materials and Methods

Patients

This was a retrospective study of all patients with thrombosed haemodialysis grafts who underwent treatment by pharmacomechanical thrombolysis or surgical thrombectomy in our hospital during the 3-year period from January 2009 to December 2011. The data was retrieved from the Radiology Department records and general hospital databases. The decision to select patients for thrombolysis or thrombectomy depended on the judgment of the vascular surgeon. Patients who had much comorbidity or who were at a high-risk for anaesthesia or surgery, and had no contraindications for thrombolysis (contrast allergy, allergy to thrombolytic drug, graft infection, history of significant gastrointestinal haemorrhage or major surgery within the prior 3 months) were selected for thrombolytic therapy. Patients with any contraindications for thrombolysis as noted above were scheduled for surgical correction. In some cases, a further consideration was the availability of an operating room, which is usually tightly scheduled. Written informed consent for the procedure was obtained from all patients after a discussion of the advantages and risks of the procedure. The present study was approved by the Ethics Committee of our institute.

Salvage Procedure

Pharmacomechanical Thrombolysis

The procedure was performed under local anaesthesia. Salvage of the thrombosed graft was performed by the pulse-spray technique by injection of recombinant tissue plasminogen activator (rt-PA) via the multi-sidehole infusion

catheter. A total dose of 10 mg of rt-PA was administered using 4 mg of loading dose via infusion catheter and forceful injections of 0.5 mg of rt-PA via infusion catheter every 30 seconds. Balloon angioplasty was performed to macerate the residual clots and treat all underlying stenoses. A final angiogram was done to assess the patency graft, arterial and venous anastomoses, venous outflow and central vein (Fig. 1).

Surgical Thrombectomy

The procedure was performed under general or regional (brachial blocking) anaesthesia. An incision was done at the venous limb of the graft and thrombectomy was performed by advancing a Fogarty thrombectomy catheter through the graft into the native venous outflow as far centrally as possible. Rigid dilators were used to dilate the venous anastomosis. A similar thrombectomy technique was directly performed on the arterial limb for the removal of the intragraft thrombus. Graft revision with patchplasty or graft interposition was performed in some patients.

Follow-up

All patients had regular haemodialysis after either the thrombolysis or thrombectomy procedures, and all were followed up at the haemodialysis centre and vascular surgery clinic. Cases of apparent graft dysfunction or failure were confirmed by a nephrologist or vascular surgeon before reoperation.

Definitions

Following the standard practice guideline published by the Society of Interventional Radiology (SIR),¹⁰ procedural success in the study was defined as restoration of flow in the dialysis graft and a palpable thrill. Additionally, less than a 30% residual diameter stenosis was a criterion included for technical success in the thrombolysis group. Primary patency was defined as the time interval after the procedure until the next access thrombosis or first subsequent intervention. Secondary patency was defined as the time

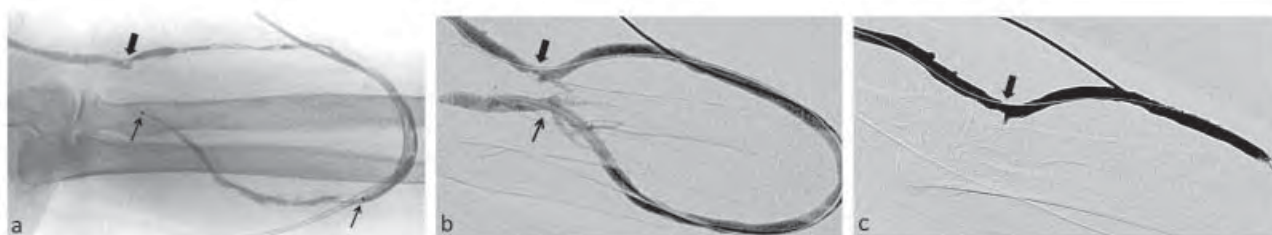


Fig 1. A 45-year-old male with a thrombosed forearm U-shaped arteriovenous graft; (a) angiogram showing intraluminal thrombus filled in entirely with intragraft and venous anastomotic stenosis (thickened arrow). Note proximal and distal markers (thin arrows) of a multi-sidehole catheter that was placed from the venous limb of the graft; (b) angiogram after thrombolysis with angioplasty showing patent arterial anastomosis (thin arrow) and intragraft with residual stenosis at the venous anastomosis (thickened arrow); (c) final angiogram after re-angioplasty showing less than 30% of residual stenosis (thickened arrow).

interval after intervention until the access was surgically declotted, revised, or abandoned. Major complications were defined as complications that required additional treatment, or resulted in permanent sequelae or death. Minor complications were defined as problems requiring no or nominal therapy with no sequelae.

Statistical Analysis

We compared patient data, graft characteristics and outcomes of the procedures between the 2 groups. All continuous data were presented as mean $\pm$ standard deviation using Student's *t*-test. Categorical data were evaluated by chi-square test. Patency rates between the 2 groups were analysed by the Kaplan-Meier test. *P* values less than 0.05 were considered to be statistically significant.

Results

A total of 108 patients with 114 thrombosed dialysis grafts were enrolled. Forty-eight patients with 50 thrombosed dialysis grafts underwent thrombolysis with balloon angioplasty and 60 patients with 64 thrombosed dialysis grafts underwent surgical thrombectomy. The mean ages of patients in the thrombolytic and thrombectomy groups were 55 ± 10 years (range, 40 to 70 years) and 57 ± 9.5 years (range, 42 to 72 years), respectively. Two patients in the thrombolytic group had 2 episodes of thrombosed graft. One and 2 patients in the thrombectomy group had 3 and 2 episodes of thrombosed graft, respectively. A forearm U-shaped graft was the most common thrombosed graft in both groups. The average time from graft thrombosis until treatment was 20 ± 15 hours in the thrombolysis group and 32 ± 12 hours in the thrombectomy group. Summaries of the patient data and graft characteristics in each group are shown in Table 1. There were no statistically significant differences between the thrombolysis and thrombectomy techniques in the procedural success rates (94% and 93.8 %,

$P = 0.15$). The mean procedural times of the thrombolysis and thrombectomy techniques were 2.0 ± 1.5 hours and 2.1 ± 1.3 hours ($P = 0.20$). The average patency times of the thrombolysis and thrombectomy groups were 6.24 months and 6.30 months ($P = 0.17$). The primary patency rates at 12 months were $28.0\% \pm 8.4\%$ for the thrombolysis group and $30.0\% \pm 6.3\%$ for the thrombectomy group ($P = 0.65$) (Fig. 2). The secondary patency rates at 12 months were $54.3\% \pm 7.8\%$ for the thrombolysis group and $57.0\% \pm 4.8\%$ for the thrombectomy group ($P = 0.49$) (Fig. 3). A small amount of perigraft haematoma was found in both groups, 30% for the thrombolysis group and 40% for the thrombectomy group ($P = 0.48$). There were no procedure-related major complications in either group.

Discussion

Since the first described use of thrombolytic drugs for the treatment of thrombosed prosthetic graft by Zeit and Cope¹¹ in 1985, this technique has been accepted worldwide with various modifications and instruments. Earlier studies have indicated that a surgical thrombectomy had overall better outcomes than the endovascular technique. Schuman et al¹² reported 67% procedural success rates with thrombolysis and 94% surgically. A prospective, randomised study by Marston et al⁴ showed a statistically significant difference in the 6-month primary patency rates, with their thrombolysis group at 11% at 6 months and the surgical thrombectomy group at 36%. However, more recent studies¹³⁻¹⁶ have showed an equivalent outcome between the 2 groups. A prospective, randomised study by Dougherty et al¹⁶ reported no statistically significant difference in the 12-month primary patency rates between the thrombolysis ($13.7\% \pm 6.6\%$) and the surgical thrombectomy groups ($26.0\% \pm 7.6\%$), nor in the mean time to graft rethrombosis between the groups (6 months vs 7 months, respectively). Our results were the same as the study by Dougherty et al¹⁶ that showed equivalent patency rate in both groups. Another recent

Table 1. Patient Data and Graft Characteristics

Parameter	Thrombolysis	Thrombectomy	<i>P</i> Value
Age (years)	55 ± 10	57 ± 9.5	0.45
Sex			0.55
Male	26	33	
Female	22	27	
Type of graft			0.39
Forearm U-shaped type	28	34	
Forearm straight type	16	22	
Arm U-shaped type	2	6	
Arm straight type	4	2	
Time interval before treatment (hours)	20 ± 15	32 ± 12	0.04

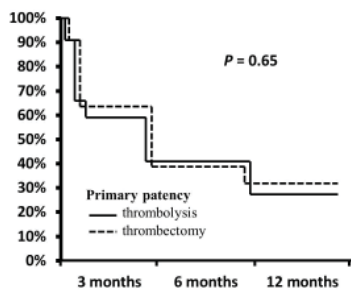


Fig 2. Kaplan-Meier curve for primary patency rate after restoration of thrombosed dialysis graft.

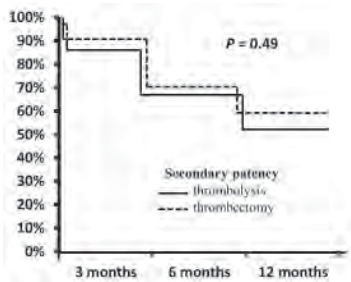


Fig 3. Kaplan-Meier curve for secondary patency rate after restoration of thrombosed dialysis graft.

study by Sofocleous et al¹⁷ using a similar endovascular technique and thrombolytic agent as ours for treatment of thrombosed dialysis graft had similar outcomes with a procedural success rate of 94% and primary and secondary patency rates of 44% and 72% at 6 months.

We think that an improvement of any instrument and technique such as using a multi-sidehole infusion catheter placed along the thrombus with a pulse-spray technique and using a rt-PA that is a potent thrombolytic drug will increase the effectiveness of clot lysis due to increased interactive surface area of the thrombus resulting in an improved outcome with the endovascular thrombolytic technique. In addition, balloon angioplasty can be used to treat any underlying stenosis in the thrombolysis group. Our study showed high procedural success rates in both groups with statistically non-significant differences (94% vs 93.8%, $P = 0.15$). However, a procedural failure involving both groups in our study was the failure to pass a guide wire or Fogarty thrombectomy catheter through the severe or occluded venous anastomosis. The time interval of graft thrombosis until treatment is another factor that affects the success of the thrombolysis technique. In our study, there was statistically significant difference in this time between the thrombolytic and thrombectomy groups (20 ± 15 hours vs 32 ± 12 hours; $P = 0.04$). We believe that an early thrombolysis of a fresh thrombus has a higher chance of procedural success.

Although these 2 procedures were not different in the outcomes of treatment, there were differences in the cost of the different procedures. Dougherty et al¹⁶ found significant differences in the mean costs for thrombolysis compared with surgical thrombectomy (US\$ 2925 vs \$1512; $P < 0.01$). In this study, we have not included the different costs of the

2 procedures in the results section; however, the total cost per patient in our institute was estimated at US\$ 1667 for thrombolysis vs only US\$ 667 for surgery thrombectomy. The main reason for these high costs in both the Dougherty et al¹⁶ and our study was the cost of the supplies, mainly the multi-sidehole catheter, the balloon catheter, and the thrombolytic drugs necessary for the procedure. The length of hospital stay in our institute was not a cost factor, as both groups were similar, with an average of 24 hours for the thrombolysis group and 24 to 48 hours for the thrombectomy group.

The most common complication of the procedures to salvage a thrombosed graft in our study was perigraft haematoma. Sands et al⁹ also reported this complication in their study with similar rates in both groups: 16% of the thrombolysis group and 11% of the thrombectomy group. Vein rupture, graft extravasation and pseudoaneurysm formation are other less common complications after a thrombolysis procedure that can be treated by an endovascular technique. One earlier study has reported an incidence of arterial embolisation of 0% to 7% with the thrombolytic technique,¹² but this complication was not reported with their surgical thrombectomy patients, possibly due to the fact that an immediate angiogram is not usually performed after a standard thrombectomy. However, clinically significant arterial embolisms can be treated by thrombo-aspiration or embolectomy. Pulmonary embolism after thrombosed graft correction is another concern. Usually, these pulmonary emboli are clinically silent and asymptomatic clots can be dissolved by autolysis. However, clinically significant pulmonary embolism has been reported.¹⁸ Other uncommon major complications have also been reported in surgical thrombectomy, including pulmonary edema and septicemia.⁹

There were some limitations in this study. Firstly, the study was a retrospective study. Secondly, the decision for doing either endovascular thrombolysis or surgical thrombectomy was dependent on the judgment of a vascular surgeon, which might have caused selection bias. Lastly, some included thrombosed AVGs had a history of multiple episodes of previous thrombosis, which could have had an impact on the patency results.

Conclusion

Our study found no differences in outcomes between patients treated with pharmacomechanical thrombolysis and surgical thrombectomy for thrombosed haemodialysis grafts. Additionally, there were no procedure-related major complications in the patients treated with pharmacomechanical thrombolysis, indicating that pharmacomechanical thrombolysis is a safe and effective procedure and can be set as an alternative option for treatment of dialysis graft thrombosis.

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Localised Dermatitic Nodules but No Itch

Dear Editor,

In 1909, Hyde first described nodular prurigo as pruritic nodules on the extensor surfaces of the lower extremities in middle-aged women. Thus, nodular prurigo is also known as Hyde's prurigo. As the name suggests, nodular prurigo is a chronic dermatosis characterised by an intensely pruritic, papulonodular eruption. We describe a patient who presented with nodular prurigo in a unilateral lower limb due to dysaesthesia and sciatica pain instead of itch.

A 53-year-old man with no known medical or dermatological problem presented to us with multiple lumps on the right lower limb. On examination, he had multiple excoriated nodules only on the right shin extending up to the thigh in the L5 dermatome suggestive of nodular prurigo (Fig.1). There was no itch but instead he complained of dysaesthesia and admitted to constant rubbing and peeling of the skin in order to get rid of the uncomfortable sensation. On further questioning, he revealed that he had been experiencing shooting pains from the buttock down to his right leg whenever he stretched his back for the last 1 year. Neurological examination of the legs revealed normal reflexes, sensation and motor function.

Routine blood tests including full blood count, renal function and liver function tests were normal. Biopsy of one of the nodules showed findings consistent with nodular prurigo. There was psoriasiform hyperplasia, irregular acanthosis with focal hypergranulosis (Fig. 2A). The



Fig 1. Prurigo nodules localised to the right lower limb.

superficial and deep vascular plexuses showed lymphocytic and plasmacytic cuffing. In addition, there was evidence of neural hyperplasia, with the clear identification of nerve trunks adjacent to the lympho-plasmacytic cuffing (Fig. 2B). Magnetic resonance imaging of the lumbosacral spine revealed degenerative disc disease affecting the lower lumbar region, worse at L4/5 (Fig. 2C). The right exiting L5 nerve root was compressed (Fig. 2D).

To our knowledge, this is the second case of a rare occurrence of nodular prurigo in an area of pain instead of itch. Batta et al¹ first described a case of nodular prurigo occurring in the same distribution as sciatic pain from a prolapsed intervertebral disc. We would like to highlight that itch may not be an essential triggering factor that leads to the formation of nodular prurigo, and that dysaesthesia and pain from radiculopathy resulting in rubbing and peeling may also lead to nodular prurigo.

Even though our patient did not experience any itch in the dermatome of the nerve compression, neuropathy is a known cause of pruritus. Neuropathic itch can originate at any point along the afferent pathway as a result of damage to the nervous system.² In a case series of 8 patients with severe nodular prurigo inadequately controlled with standard therapy and were considered for treatment with thalidomide, 5 patients showed evidence of peripheral neuropathy on nerve conduction studies.³ This suggested that nodular prurigo may be associated with an underlying peripheral neuropathy in a subset of patients.

The aetiology of nodular prurigo remains unknown. There is uncertainty as to whether nodular prurigo is a primary cutaneous disease or whether it is a pathological reaction secondary to pruritus and scratching. We propose that in some cases, nodular prurigo is a secondary phenomenon as our patient developed this dermatosis from constant rubbing and peeling without any primary cutaneous disease.

To study the mechanism of discogenic pain, Jung et al⁴ analysed the serial expression of pain-related molecules in the dorsal root ganglia and thalamus using a newly developed rat model of disc degeneration and found that the expression of glial cell line-derived neurotrophic factor, calcitonin gene-related peptide and substance P were significantly increased. Previous immunohistochemical studies in nodular prurigo has demonstrated proliferation of substance P and calcitonin

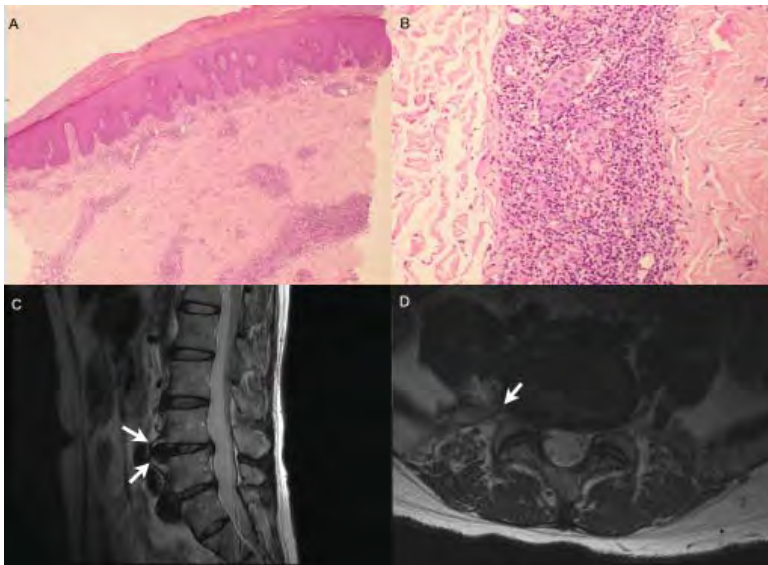


Fig 2. (A) Histopathology showing psoriasiform hyperplasia, irregular acanthosis with focal hypergranulosis (H and E, original magnification x 40). (B) Lymphocytic and plasmacytic cuffing around the neurovascular bundles (H and E, original magnification x 200). (C) Magnetic resonance image of the lumbosacral spine revealed degenerative disc disease affecting the lower lumbar region, worse at L4/5 region (arrows). (D) The right exiting L5 nerve root is compressed (arrow).

gene-related peptide as well.⁵ These neuropeptides mediate the cutaneous neurogenic inflammation and enhance the proliferation of fibroblasts and keratinocytes, which then lead to nodular prurigo.

Our patient was started on topical betamethasone dipropionate cream and was referred to the orthopaedic surgeon. He received a right L4/L5 transforaminal epidural steroid injection. His dysaesthesia resolved and the nodules on the right leg were significantly flatter 1 month later. The course of prurigo nodularis is often chronic, and some patients respond very poorly to the standard therapeutic modalities. The treatment of prurigo nodularis can be disappointing and frustrating for both the patients and physicians. Early identification of the underlying neuropathy in our patient led to quick relief of the symptoms and dermatitic nodules.

In conclusion, we describe a case of localised dermatitic nodules which led to a diagnosis of L5 radiculopathy. Nodular prurigo may be a secondary phenomenon due to nerve root compression and patients with localised nodular prurigo in a dermatomal distribution should be evaluated for the possibility of underlying neuropathy.

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Ultrasound-Guided Thyroid Fine Needle Aspiration Biopsy—The Way Forward

Dear Editor,

I read with great interest the recent article published in the *Annals of Academy of Medicine Singapore* entitled, 'Surgeon-Performed Ultrasound-Guided Fine Needle Aspiration Cytology (SP-US-FNAC) Shortens Time for Diagnosis of Thyroid Nodules, *Ann Acad Med Singapore* 2014;43:320-4'. Indeed, ultrasound-guided fine-needle aspiration (US-FNA) is an exceptionally valuable and simple approach for the diagnosis of thyroid nodules, and has a much higher sensitivity and specificity compared to conventional palpation-directed biopsy techniques. Non-radiologists (surgeons, endocrinologists or sonographers) are also increasingly involved in US assessment and US-FNA of thyroid nodules, which translates into shorter waiting time for the patient and greater patient satisfaction. Many recent epidemiological studies have shown the rapidly rising incidence of thyroid cancers despite stable low mortality rates of such cancers.^{1,2} Most of the increase was contributed by the rise in the diagnosis of small papillary thyroid cancers, which generally have an indolent course and a favourable long-term prognosis.

Intriguingly, Brito et al¹ have recently proposed that overzealous use of imaging and biopsies by clinicians contributed to this trend. Hence, many professional bodies have strived to produce guidelines to aid clinical decisions in the selection of thyroid nodules for US-FNA, recommending only nodules with suspicious ultrasound characteristics be biopsied.³ Although no single ultrasound characteristic can confidently predict malignancy in the assessment of thyroid nodules, the presence of several suspicious ultrasound features generally provides excellent accuracy in such predictions. The authors in the paper quoted a non-diagnostic rate of 30% in their institution, which was partly attributed to the initial lack of experience in this procedure. In our experience, the presence of a cytotechnologist on-site examining the specimen have been shown to improve diagnostic adequacy through improved sampling, and have largely contributed to a consistent non-diagnostic rate of below 10%. One of the main advantages of on-site assessment is that it allows additional material to be aspirated if the sample is insufficient or if material is needed for ancillary tests.⁴ Furthermore, the presence of a trained biomedical scientist enables good quality preparations to be made. The sampling of nodules with

large cystic components could have also accounted for the authors' higher non-diagnostic rates. The cystic component of the thyroid nodule has been shown to be an independent predictive factor for non-diagnostic specimens.⁵ However, repeat US-FNA often provides an adequate specimen and should be the standard approach to such nodules, given their potential risk of malignancy.

In summary, US-FNA is an excellent modality for the assessment of thyroid nodules. However, clinicians should be aware of the pitfalls of over-diagnoses of such nodules. Non-diagnostic FNAs remain a significant challenge in the evaluation of thyroid nodules and should be communicated with the patient, especially if the nodule in question is particularly cystic. Lastly, the presence of ancillary on-site support has been shown to increase sampling adequacy and should be employed whenever possible.

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Avulsed Tip of a Systemic Iceberg

An 18-year-old male presented to the emergency department of Khoo Teck Puat Hospital with knee pain and swelling while playing basketball. He was unable to bear weight. He had a surgical history of combined liver and kidney transplant 3 years ago.

What do the radiographs of the left knee (Figs. 1A and 1B) and previous skeletal survey radiographs (Figs. 2A and 2B) show? What is the diagnosis?

- A. Renal osteodystrophy
- B. Lead poisoning
- C. Osteopetrosis
- D. Hyperoxaluria
- E. Treated leukaemia

Findings and Diagnosis

Frontal and lateral radiographs of the left knee show an avulsion fracture involving the inferior pole of the patella (Figs. 1A and 1B). The bones were diffusely osteopenic with lucent metaphyseal bands involving proximal tibia, fibula and distal end of femur with adjacent dense sclerotic bands. The previously done skeletal survey revealed end-plate sclerosis of lumbar vertebral bodies (Fig. 2A) and lucent metaphyseal bands in distal radius, ulna and small



Fig. 1. (A) Antero-posterior and (B) lateral radiographs of the left knee taken at admission.

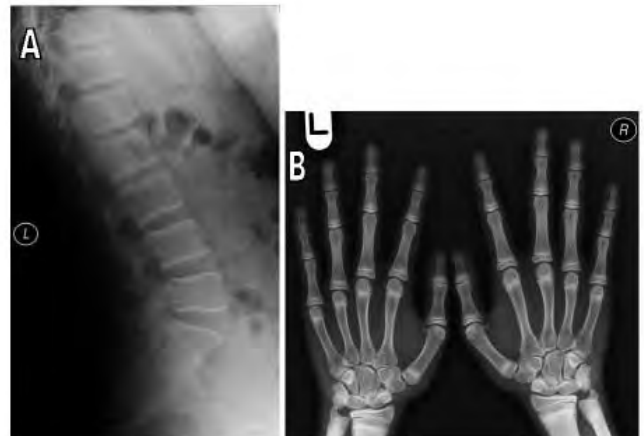


Fig. 2. Previous radiographs (obtained 3 years ago) of the (A) lumbar spine and (B) both hands.

tubular bones of hands with subjacent dense sclerotic bands (Fig. 2B). The patient also had bilateral renal cortical nephrocalcinosis (Fig. 3). Subsequent investigations included: serum creatinine 841 $\mu\text{mol/L}$ (65 to 125), 24-hour urine oxalate 1.89 mmol/day and parathyroid hormonal levels 31.0 pmol/L (1.3 to 7.6). Renal biopsy was done which revealed oxalate calcifications within the tubular lumens with moderate to marked tubular atrophy consistent with renal tubular oxalosis. Genetic analysis revealed mutation of the alanine-glyoxylate amino transferase (*AGXT*) gene. The diagnosis was primary hyperoxaluria.

Discussion

Primary hyperoxaluria (PH) is an uncommon autosomal recessive disease which occurs in 1 in 60,000 to 120,000 live births and affects glyoxylate metabolism.¹⁻³ It is classified into 3 types: PH1, seen in 80% of patients, occurs due to mutation of the *AGT* gene resulting in deficiency of the enzyme alpha-ketoglutarate/glyoxylate carboligase present in the hepatocyte peroxisomes. PH2 represents 10% of cases and results from deficiency of glyoxylate reductase enzyme, and PH3 occurs in 10% of cases due to mutation of *HOGA1* gene causing deficiency of hydroxyl-oxoglutarate aldolase enzyme.^{1,4,5} In PH1 and PH2 presentations, patients develop

Answer: D

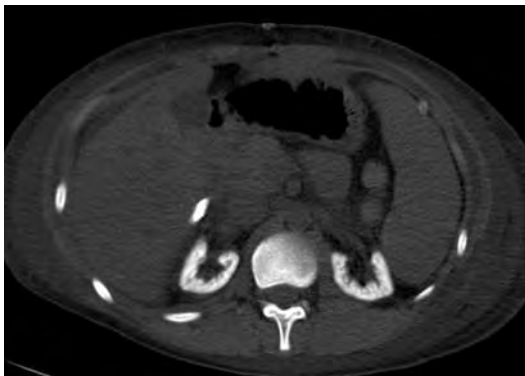


Fig. 3. Axial non-contrast computed tomography image showing deposition of calcium oxalate as homogeneous cortical calcification in both kidneys in keeping with nephrocalcinosis.

end-stage renal disease due to increased levels of oxalate and glycolate in the circulation.⁴ In PH3, although there is urinary oxalate elimination, progression to end-stage renal disease has not been reported.⁵

Patients with PH typically present in childhood, with median age being 5 years.¹ Children commonly present with symptoms of recurrent nephrolithiasis. Eventually, patients develop renal failure due to nephrocalcinosis, secondary interstitial fibrosis and infection secondary to urolithiasis.⁶ PH affects renal function resulting in deposition of highly insoluble calcium oxalate crystals in extra-renal tissue. These crystals then incite inflammatory reaction and cause tissue damage.^{6,7} Although oxalate deposition can occur in various organs like blood vessels, central nervous system, eyes, skin, peripheral nerves and even the intestine, imaging is useful for detecting renal and musculoskeletal involvement.⁶

For early diagnosis and to prevent end-stage renal disease in patients with suspected PH, it is essential to get a thorough family history along with oxaluria tests like 24-hour urine glycolate and oxalaemia. In uncertain cases, histological studies, especially renal biopsies, which can demonstrate oxalate crystals, are very useful. Genetic analysis is required to categorise the mutational variant and confirm the diagnosis.⁵

In the musculoskeletal system, the radiographic spectrum of PH is influenced by factors affecting bone metabolism and includes high levels of calcium oxalate, secondary hyperparathyroidism and renal osteodystrophy.⁶ The earliest radiographic features are dense metaphyseal bands affecting the extremities of long bones. In contrast to renal osteodystrophy, dense metaphyseal bands of oxalosis develop rapidly, are homogeneous and of greater density. This is due to dense oxalate crystals superimposing on already increased bone density of secondary hyperparathyroidism.^{4,8} With disease progression, oxalate crystals deposited in the

metaphyseal band incite an inflammatory reaction. This inflammatory reaction causes bone resorption; as a result, bones later develop wide translucent metaphyseal zones adjacent to or within previously seen dense metaphyseal bands.^{4,6} Other radiologic features which may be seen in patients with PH are diffuse osteosclerosis, rugger jersey spine, subperiosteal bone resorption, acro-osteolysis, vascular and soft tissue calcification. These findings are primarily due to secondary hyperparathyroidism and renal osteodystrophy. Other skeletal manifestations in paediatric patients are delayed skeletal maturation, pathological fractures and epiphyseal injuries which can affect their growth and development.¹

Another organ that is commonly affected is the kidney. Any young child presenting with recurrent urolithiasis and bilateral cortical nephrocalcinosis should be investigated further for possible PH. Renal damage occurs due to recurrent nephrolithiasis, infection secondary to urolithiasis, nephrocalcinosis and interstitial fibrosis.⁶ Conventional radiographs and ultrasound imaging together can help identify cortical nephrocalcinosis, renal or ureteric stones and complications like hydronephrosis and pyelonephritis.¹ The only curative treatment for PH is combined kidney-liver transplantation.⁴

Conclusion

It is important to be aware of skeletal and other systemic imaging manifestations of PH for early diagnosis, as patients with this condition can now benefit from longer survival due to newer treatment methods such as combined kidney-liver transplantation.

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